Dissertation on

"STUDY ON THE ROLE OF HBA1C AS A PROGNOSTIC FACTOR IN TYPE 2 DIABETES PATIENTS WITH SEPSIS"

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CERTIFICATE

This is to certify that the dissertation titled **"STUDY ON THE ROLE OF HBA1C AS A PROGNOSTIC FACTOR IN TYPE 2 DIABETES PATIENTS WITH SEPSIS"** is the bonafide original work done by **Dr.K.LAVANYA** , post graduate student , Institute of Internal medicine , Madras Medical College, Chennai – 3 , in partial fulfilment of the University Rules and Regulations for the award of MD Branch – 1 General Medicine, under our guidance and supervision, during the academic year 2014 – 2017.

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DECLARATION

I**, Dr. K. LAVANYA** solemnly declare that dissertation titled **"STUDY ON THE ROLE OF HBA1C AS A PROGNOSTIC FACTOR IN TYPE 2 DIABETES PATIENTS WITH SEPSIS"** is a bonafide work done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai- 3 during April 2016 to September 2016 under the guidance and supervision of my unit chief **Prof.P.VIJAYARAGHAVAN**, **M.D & Prof.S.MAYILVAHANAN M.D.,** To be submitted to the Tamilnadu Dr.M.G.R.Medical University towards partial fulfilment of requirements for the award of **M.D. DEGREE IN GENERAL MEDICINE BRANCH – I.**

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ABBREVIATIONS

CRP	-	C Reactive Protein
APACHE II	-	Acute Physiology and Chronic Health Evaluation
SOFA	-	Serial Organ Failure Assessment test
MODY	-	Maturity-Onset Diabetes of the Young
OGTT	-	Oral Glucose Tolerance Test
FFA	-	Free Fatty Acids
TNF-α	-	Tumour Necrosis Factor alpha
IL-6	-	Interleukins - 6
PAI-1	-	Plasminogen Activator Inhibitor - 1
BMI	-	Body Mass Index
DCCT	-	Diabetes Control and Complications Trial
UKPDS	-	United Kingdom Prospective Diabetes Study
vWF	-	von Willebrand Factor
PGI	-	Prostacyclin
NAD	-	Nicotinamide Adenine Dinucleotide

NADH	-	Nicotinamide Adenine Dinucleotide Hydrogenase
AGES	-	Advanced Glycated End Products
DKA	-	Diabetic KetoAcidosis
OHA	-	Oral Hypoglycemic Agents
MODS	-	Multi Organ Dysfunction Syndrome
SIRS	-	Systemic Inflammatory Response Syndrome
GIT	-	Gastro Intestinal Tract
NK cells	-	Natural Killer Cells
TLR	-	Toll Like Receptors
NO	-	Nitric Oxide
AKI	-	Acute Kidney Injury
DIC	-	Disseminated Intravascular Coagulation
ACTH	-	AdrenoCortico Trophic Hormone
MAP	-	Mean Arterial Pressure
PEEP	-	Positive End Expiratory Pressure

CONTENTS

INTRODUCTION

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders characterised by chronic hyperglycemia associated with disturbances of carbohydrate, fat and protein metabolism[2]. It causes long term damage and dysfunction to all the organs of the body especially kidneys, eyes, nerves, blood vessels and heart[2].

It's a well known fact that people with diabetes have increased frequency and severity of infections. The most important factor responsible for increased incidence and severity are related to organ dysfunction and impaired immune defence mechanisms[1,20,21] .

Elevated plasma glucose levels in the hospitalized patients are affected by several factors like glucose level before the onset of illness, acute stress and time at which the sample is taken and drug intake. However glycated haemoglobin (HbA1c), which is formed in the process of non-enzymatic glycation[1] reflecting chronic glucose control over the past 3 months is less affected by these factors[2].

There are few studies which say that HbA1c is an important predictor of mortality in type 2 diabetes patients with sepsis[1]. Hence this study is to assess whether HbA1c can be used as a prognostic factor in diabetes patients with sepsis in future.

AIMS AND OBJECTIVES

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PRIMARY OBJECTIVE

To evaluate the predictive value of HbA1c for hospital mortality and length of stay in patients with type 2 diabetes admitted with sepsis.[1]

SECONDARY OBJECTIVE

To study the correlation of HbA1c with other factors like admission blood sugar, CRP, APACHE II, SOFA score and assessing the efficacy of HbA1c as a prognostic factor.[1]

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Diabetes mellitus is a group of metabolic disorder characterised by chronic hyperglycemia due to absolute or relative deficiency in insulin secretion and or its action.[2] It causes damage to all the organs in the body specifically eyes, nerves, blood vessels, heart and kidneys.[2]

ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS:[2]

A) TYPE 1

Beta cell destruction leading to absolute deficiency of insulin. It can be either

1. Idiopathic
2. Autoimmune

B) TYPE 2

1. Predominantly insulin secretory defects
2. Predominantly insulin resistance

C) OTHER SPECIFIC TYPES OF DIABETES

1. Genetic defects – beta cell dysfunction eg.MODY 1 to 6
2. Genetic defects – insulin action eg. type A insulin resistance
3. Diseases of exocrine pancreas eg. fibrocalculus pancreatopathy
4. Endocrinopathies eg. cushings, acromegaly

5. Drug induced eg.glucocorticoids
6. Infections eg. congenital rubella
7. Uncommon forms of immune mediated diabetes eg. stiff man syndrome
8. Other genetic syndromes

D) GESTATIONAL DIABETES MELLITUS

STAGES OF DIABETES:[2]

There are various stages of diabetes

1. Normal glucose tolerance
2. Impaired glucose tolerance or impaired fasting glucose
3. Diabetes mellitus which may be
    a. Non insulin requiring
    b. Insulin requiring for control
    c. Insulin requiring for survival

DIAGNOSIS OF DIABETES MELLITUS:

Diabetes is diagnosed when the fasting plasma glucose is above 126 mg% or random blood glucose more than 200 mg% on more than one occasion.[2]

OGTT is applied for diagnosis of diabetes. This is the only test to diagnose impaired glucose tolerance. OGTT is done after 10 to 16 hrs of overnight fasting (during which water may be taken) in the morning .It should be done after 3 days of unrestricted diet. The diet consists of more than 150 grams of carbohydrates to sensitize the beta cells of pancreas.[2]

TEST:

A fastig blood sample is taken before glucose load is given to patient. The subject then given 75 grams of glucose in 250 -300 ml of water andits given over a period of 5 minutes.[2]

OGTT DIAGNOSTIC VALUES:[2]

	Plasma glucose in mmol/lit	**Plasma glucose in mg/dl**
DIABETES MELLITUS:		
Fasting value	>=7	>=126
2 hr after glucose load	>=11.1	>=200
IMPAIRED GLUCOSE TOLERANCE TEST:		
2 hr after glucose load	7.8 - 11.0	140 – 199
IMPAIRED FASTING GLUCOSE:		
Fasting value	5.6 - 6.9	>=100 - <=125
2hr after glucose load	<7.8	<140

AETIOPATHOGENESIS OF DIABETES MELLITUS:

The abnormalities responsible for the hyperglycemia leading to diabetes mellitus is classified into 3 types:[2]

- Impaired pancreatic insulin secretion
- Peripheral resistance to insulin action occurring mainly in liver and muscle
- Excessive hepatic glucose output

IMPAIRED PANCREATIC INSULIN SECRETION:

Normal fasting insulin level is between 5 and 15 mu/ml. Insulin is normally secreted in a pulsatile manner. It is also secreted in response to meals and secretogogues. The pulsatile secretion is known as ultradian oscillations. It occurs every 90 to 120 mts and the secretion increases after food intake. In addition to this, level of insulin increases every 8 to 16 minutes in the beta cell. This helps to decrease the hepatic glucose output.[2]

Following glucose load, insulin secretion occurs as biphasic response. First phase is due to release of insulin which is stored in the granules. This is mainly responsible for suppressing hepatic glucose output. It occurs within 4 to 5 minutes interval and return to normal level within 10 minutes period. The second phase occurs due to ambient rise in

the glucose level, which is responsible for usage of glucose by peripheral tissues like adipose tissues and muscles.

INSULIN RESISTANCE AS A PRIMARY DEFECT:

There are three phases which leads to development of insulin resistance.

First phase:

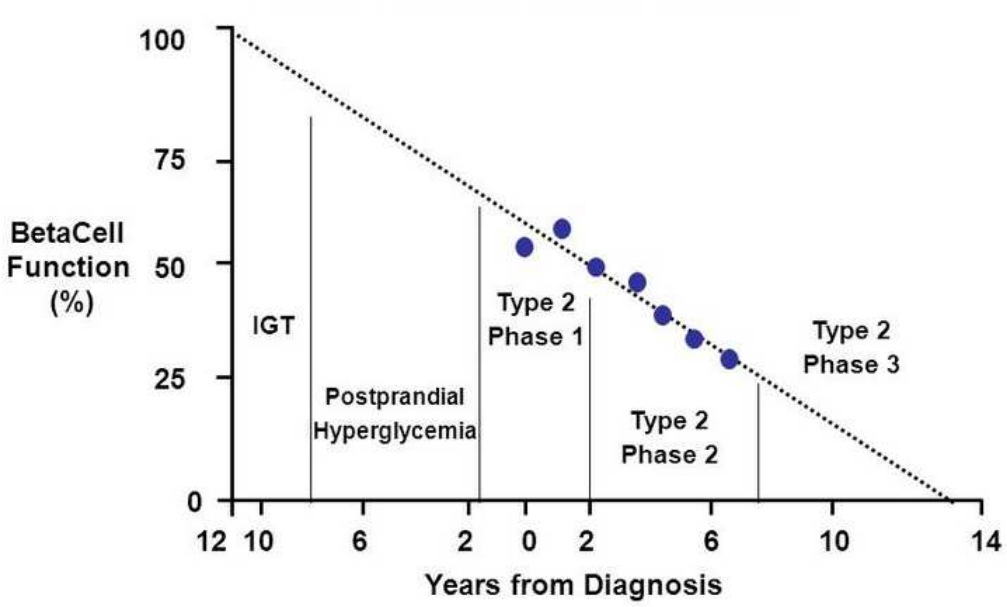
Insulin level increases and maintains blood glucose in the normal range despite demonstrable insulin resistance[2]

Second phase:

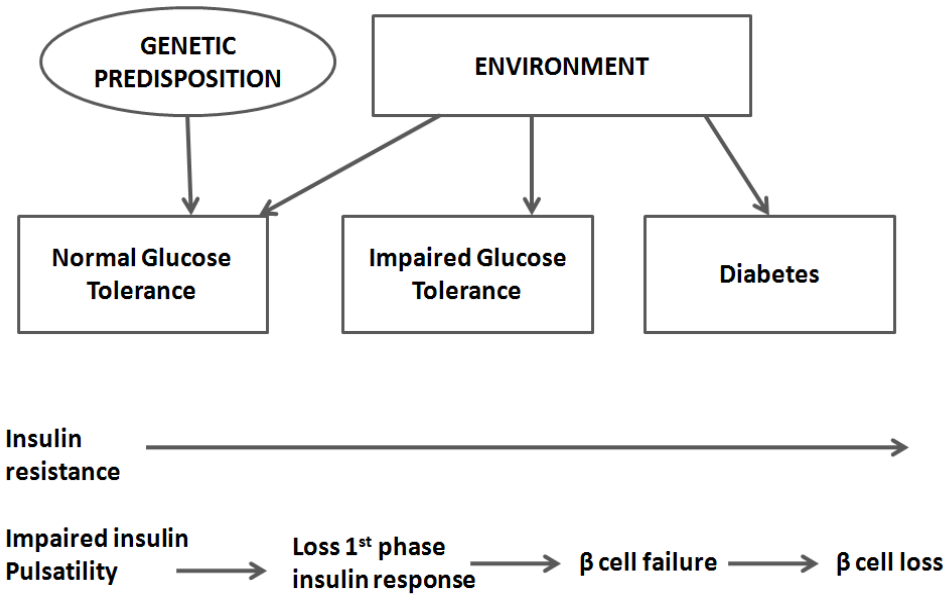
Post-prandial hyperglycemia develops even after compensatory increase in insulin level due to further worsening of insulin level.

Third phase:

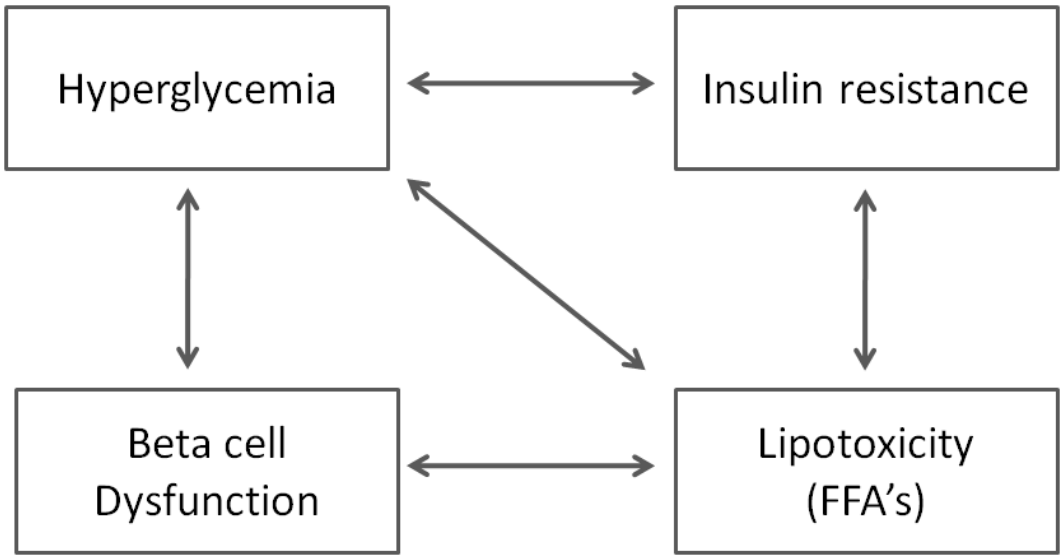
Fasting hyperglycemia develops due to decreased insulin secretion and level of insulin resistance is same as second phase.



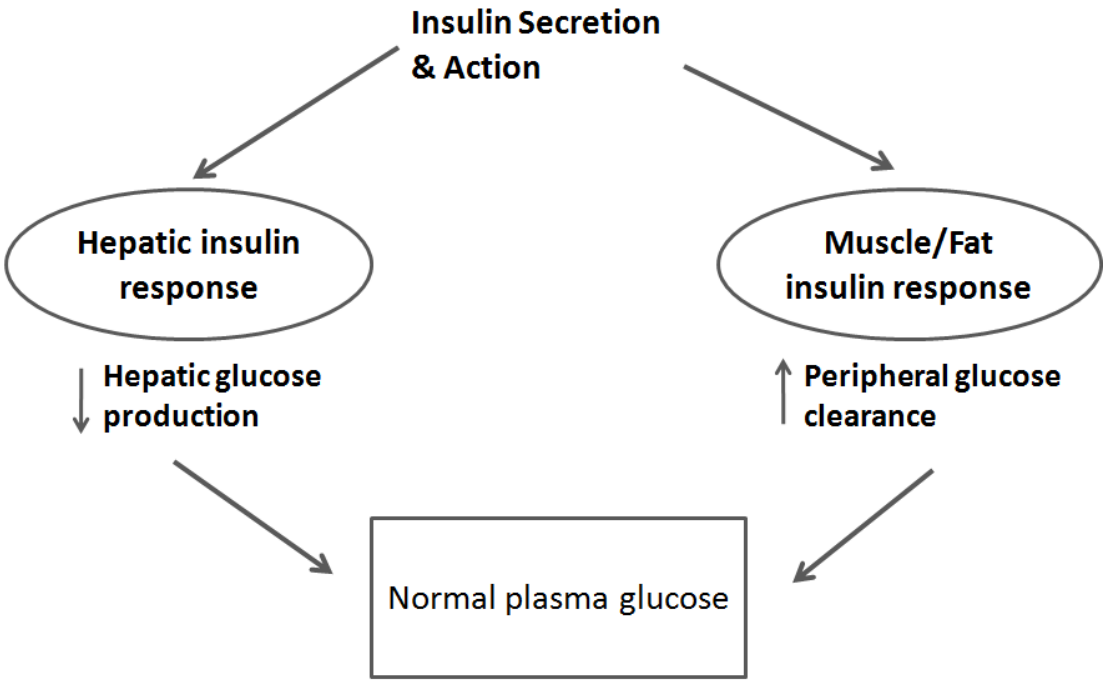
INSULIN SECRETORY DEFECT AS A PRIMARY EVENT



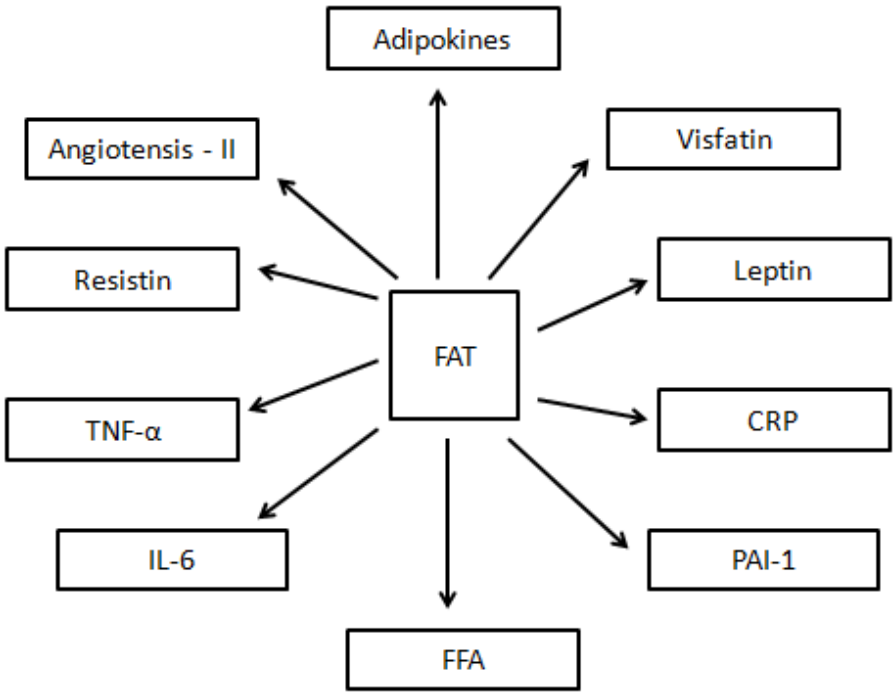
HYPERGLYCEMIA BOTH CAUSE AND EFFECT OF DIABETES



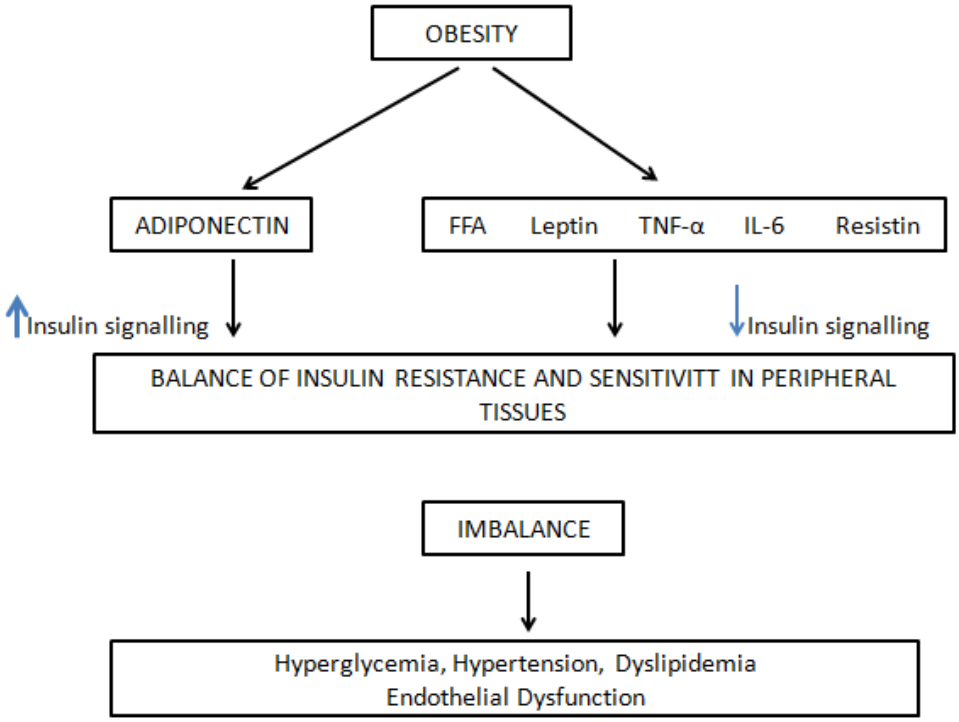
NORMAL REGULATION OF PLASMA GLUCOSE



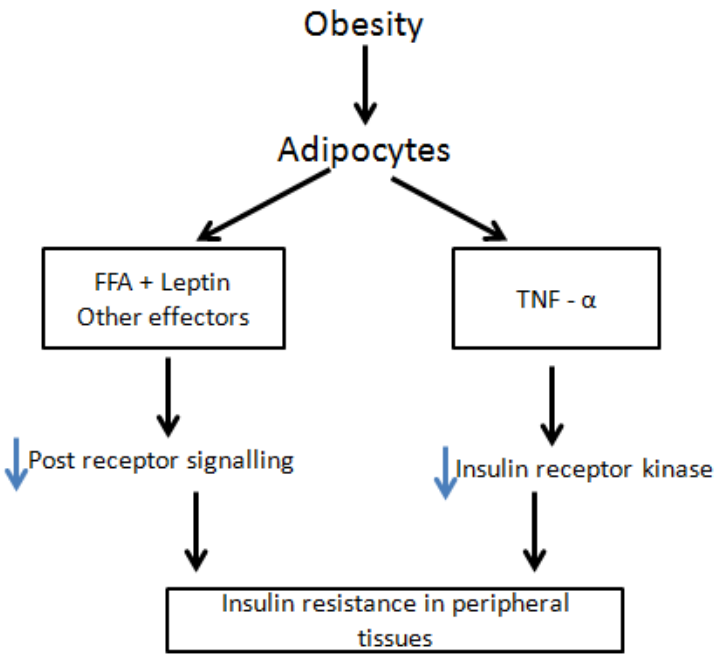
LIPOTOXICITY:



ROLE OF SECRETION OF ADIPOCYTES IN INSULIN RESISTANCE:



FFA INITIATES INSULIN RESISTANCE – MECHANISM:



MONITORING CONTROL OF DIABETES MELLITUS:

A) AIMS FOR MONITORING:

1. Symptomatic relief for ex: polyuria, polyphagia and polydipsia[2]
2. To maintain blood sugar value in the normal range and to prevent hypoglycemia[2]

B) ASSESSMENT OF DIABETES CONTROL:

1. Based on symptoms
2. Weight changes based on BMI
3. Biochemical tests:[2]

- Tests to assess diabetes control in the present state:
  - by monitoring blood glucose
- Tests to assess diabetic control retrospectively:[2]
  - Immediate past over few hours: urine glucose testing
  - Remote past:
- Few weeks: glycosylated albumin,fructosamine
- Few months: glycosylated hemoglobin

GLYCOSYLATED HEMOGLOBIN:

Glucose gets bound to haemoglobin by means of slow non-enzymatic process and results in the formation of glycosylated hemoglobin. It’s a continuous and irreversible process. It’s called

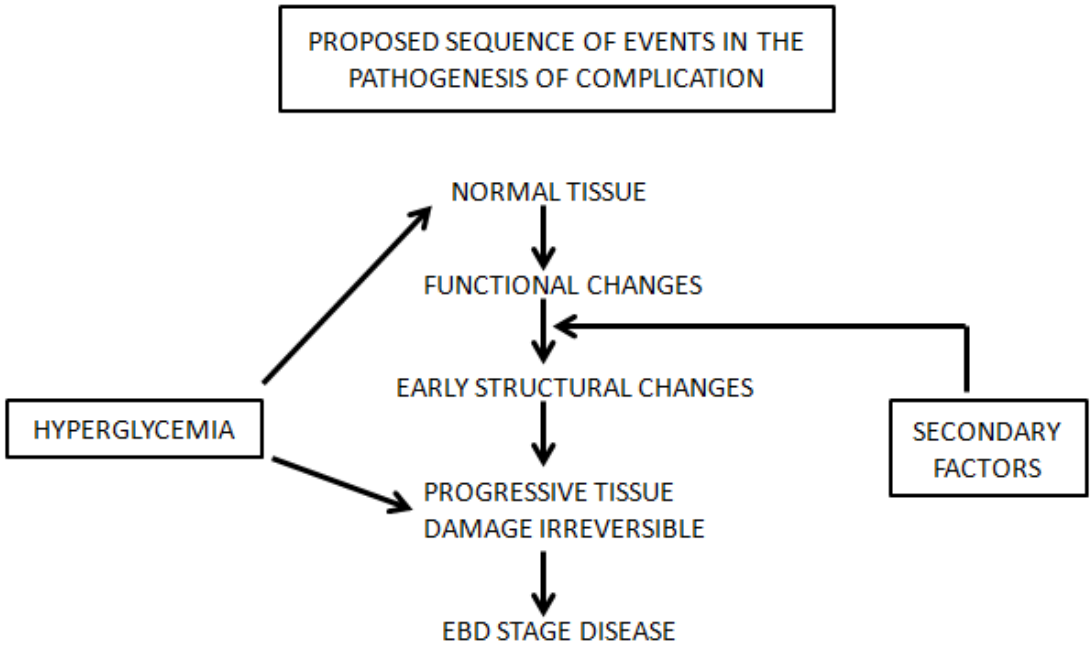
HbA1c.The amount of HbA1c formed is directly proportional to the average concentration of glucose in the blood. Lifespan of erythrocyte is around 120 days. So HbA1c reflects the average glucose level over a previous 3 months.[5] The greatest advantage is that it is not influenced by mode of therapy, physical activity, diet, relation to meals and patient cooperation at the time of testing. Its values are misleading in certain conditions like haemolytic disorders and hemoglobinopathies. Its value is higher in patients with iron deficiency anemia. It also helps to differentiate pre-existing diabetes from stress hyperglycemia.

HbA1C (%)[7]	**Mean plasma glucose (mg/dl)[7]**	**mmol/L[7]**
3	135	7.5
7	170	9.5
8	205	11.5
9	240	13.5
10	275	15.5
11	310	17.5
12	345	19.5

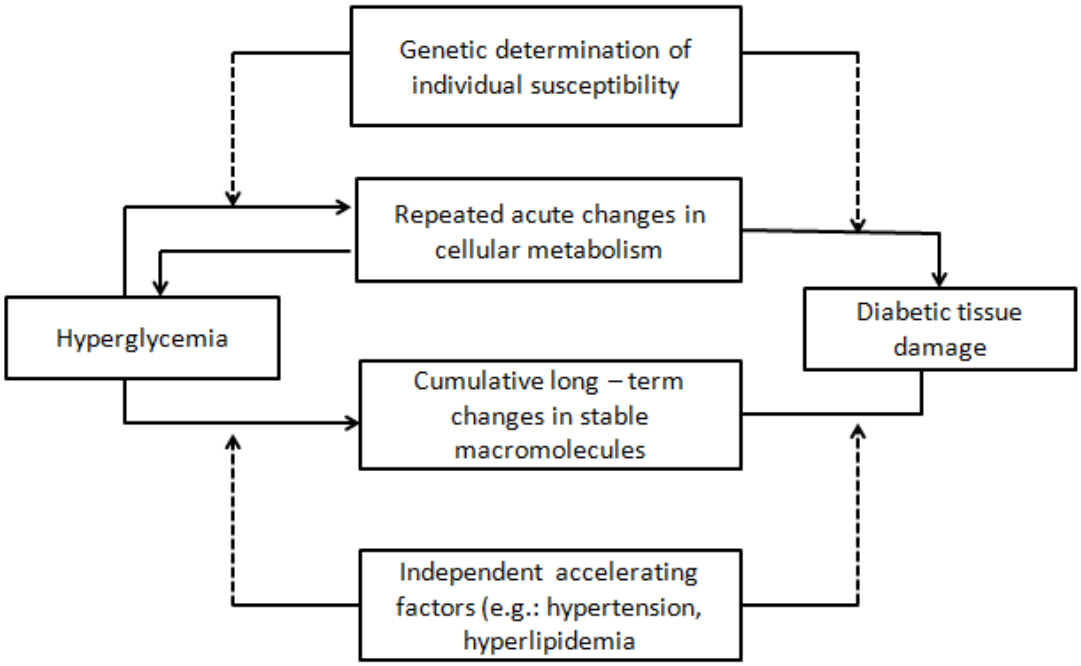
PATHOGENESIS OF DIABETES COMPLICATIONS:

Hyperglycemia is the single most cause of all chronic complications in diabetes which is proven by both DCCT- Diabetes control and complications trial, UKPDS TRIAL – United Kingdom prospective diabetes study

SEQUENCE OF EVENTS LEADING TO CHRONIC COMPLICATIONS OF DIABETES:



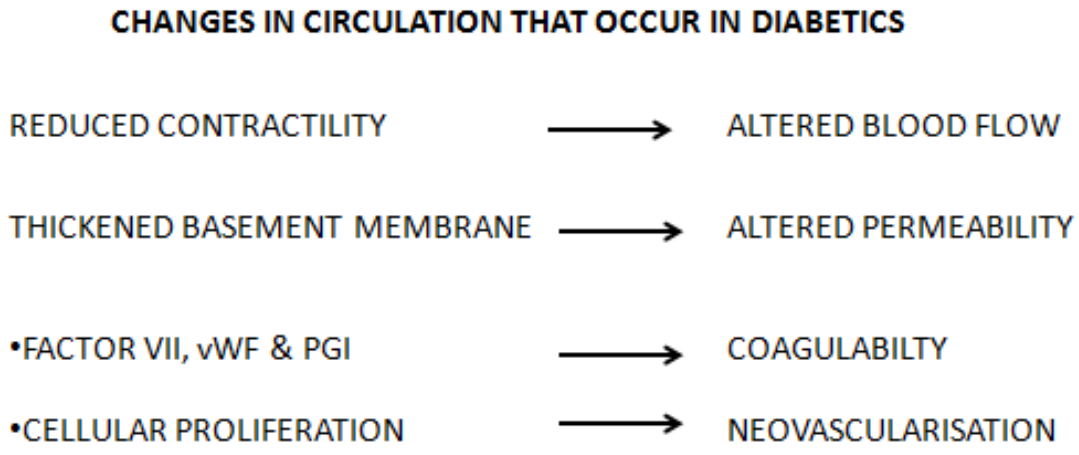
INTERACTION OF HYPERGLYCEMIA AND OTHER RISK FACTORS:



There are two factors responsible for the pathogenesis of complications:

1. Vascular changes
2. Metabolic changes

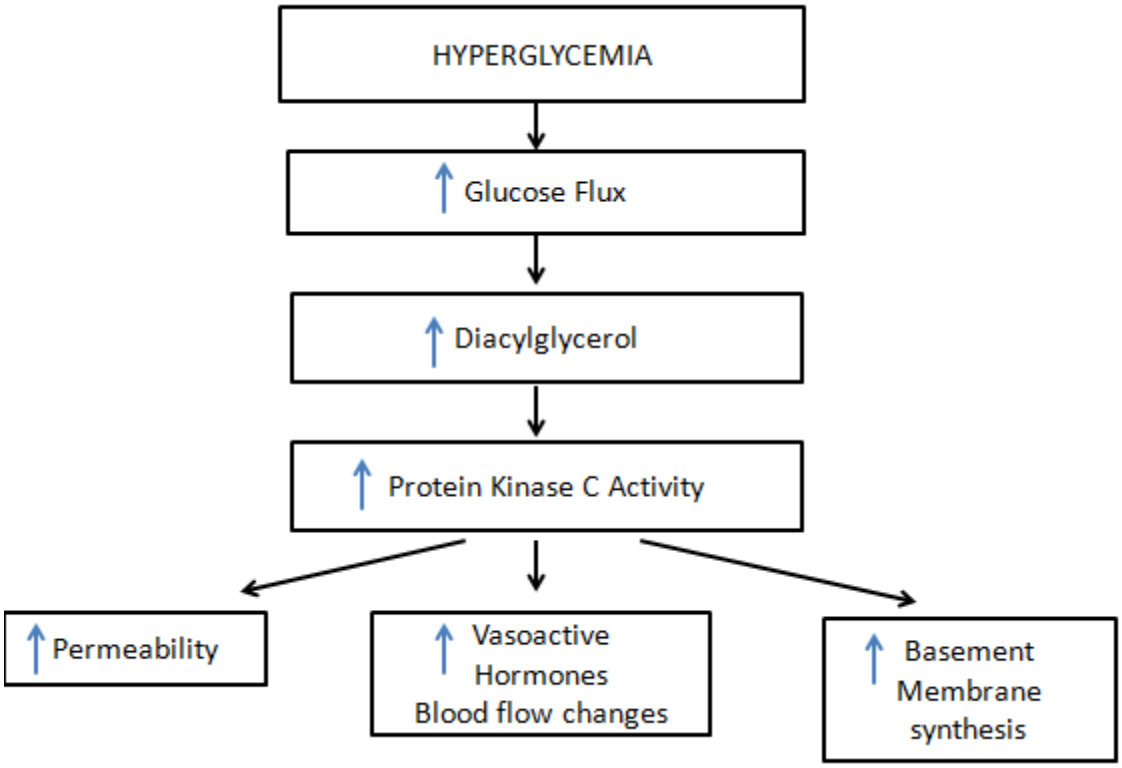
VASCULAR CHANGES:



METABOLIC CHANGES:

1. ALDOSE REDUCTASE ACTIVITY- redox changes takes place. Diabetes causes activation of polyol sorbitol pathway.In this pathway glucose is converted to sorbitol by aldose reductase, which is further converted to fructose by sorbitol dehydrogenase enzyme[2].In second step NAD is reduced to NADH.[2] Aldose reductase enzyme has very low affinity to glucose so when glucose accumulates, it increases the activity of aldose reductase that leads to increase in the sorbitol concentration.

2. DIACYLGLYCEROL - PROTEIN KINASE C ACTIVATION



3. FORMATION OF AGES – ADVANCED GLYCATED END PRODUCTS:[6]

Glucose combines with proteins non-enzymatically to form Schiff base which undergoes rearrangement to form amadori product.[2] This is reversible reaction. Cross linking of amadori product occurs to form advanced glycation end product[6] and it is irreversible reaction.

4. FORMATION OF REACTIVE OXYGEN SPECIES

COMPLICATIONS:

Complications are classified as microvascular and macrovascular. The microvasular complications are diabetic neuropathy,nephropathy and retinopathy.The macrovascular complications are ischemic heart disease, peripheral vascular disease and cerebrovasular disease.

IMPACT OF DIABETES MELLITUS ON SEPSIS:

There are 6 factors responsible for exacerbating infections in diabetic.

1. Malnutrition
2. Dehydration
3. Vascular insufficiency
4. Impaired neutrophils function [16,17] , platelets dysfunction [18,19]
5. Neuropathy
6. Humoral factors: defective gamma globulin, complement and antibody formation

Glycosylation of immunoglobulins in poorly controlled diabetic causes infections. Diabetic complications per se predispose to infections. Ex.microangiopathy causes disturbance in tissue perfusion which causes delay in wound healing. Peripheral neuropathy leads to foot trauma which predispose to secondary infections. These infections are difficult to treat

because of poor peripheral circulation. Autonomic neuropathy causes bladder dysfunction and stasis which is responsible for urinary tract infections. Glycosuria and catheterisation are additional risk factors. Frequent hospitalisation increases the risk of acquiring nosocomial infections. In DKA ketone bodies increases the level of serum iron and this causes the growth of bacteria and fungi.

DIABETES MELLITUS AND ASSOCIATED INFECTIONS

Infection Associated with Diabetes Mellitus

1. Proven Association
    a. Bacteriuria in females: 4 fold increase
    b. Tuberculosis: 3-16 fold increase
    c. Malignant otitis externa 100%
    d. Necrotizing cellulitis 75%
    e. Emphysematous cystitis 80%
    f. Emphysematous pyelonephritis 72%
    g. Acute papillary necrosis 57%
    h. Emphysematous cholecystitis 38%
    i. Peri nephric abscess 36%
2. Probable association
    a. Acute necrotizing periodontitis
    b. Cellulitis of hand or foot
    c. Gram negative pneumonia (klebsiella)
    d. Foot ulcer related infections
    e. Fungal urinary tract infections
3. Possible association
    a. Staphylococcal pneumonia
    b. Liver abscess
    c. Bacteraemia: Staphylococcal, Group B streptococcal
    d. Mucocutaneous candidiasis
    e. Osteomyelitis
    f. Fournier's gangrene
    g. Cryptococcosis, histoplasmosis, blastomycosis coccidicomycosis
    h. Carbuncles and boils
4. Proven no association
    a. Hepatitis B
    b. Bacteriuria males
    c. Pneumococcal pneumonia

EFFECT OF INFECTION ON DIABETES:

Viral infections affecting pancreatic islets (mumps and coxsackie plays a role in development of type 1 diabetes mellitus.[2] Secondary infections in diabetic aggravate hyperglycemia and increases the risk of DKA. When sudden increase in insulin requirements occurs one must rule out occult infection in diabetes. A chronic infection precipitates insulin resistance. Rarely gram negative septicaemia and pseudomonas infections causes hypoglycaemia because gluconeogenesis is inhibited by bacterial toxins.

PREVENTION AND TREATMENT PRINCIPLES:

Glycemic control is the foremost prevention and treatment option in diabetes patients with sepsis.[2,12,13,14] Patients who are properly treated with OHA's and/or insulin are less likely to develop complications even if they develop infections and sepsis. It also decreases mortality due to complications. HbA1c is used as a prognostic factor based on this aspect and it is used to assess outcome of diabetic patients with sepsis. Infections and sepsis in diabetic patients should be diagnosed early and treated with appropriate antibiotics, insulin therapy and surgical methods if needed.

SEPSIS:

Sepsis is a clinical syndrome occurs as a complication of a serious infection and it is associated with significant mortality and morbidity. The cytokine storm is induced by the focus of infection which produces series of systemic insults like generalised vasodilatation, increased capillary permeability, leukocyte infiltration. All these processes finally results in tissue damage in the entire body. Severe sepsis leads to MODS "multi organ dysfunction syndrome" and it has very high mortality even in developed countries. Severe sepsis is still a killer disease despite all the recent advances in the medical field.

Sepsis is a condition with wide varied manifestations and it's a major challenge to health care providers. The definitions, incidence, etiology, pathogenesis and outcome are discussed below.

HISTORY OF SEPSIS:

Hippocrates (460-370 BC) introduced the word "SEPSIS" .It is derived from the greek word sipsi "make rotten".[8] The coincidence of blood putrefaction ie.septicemia and fever was first observed by Ibn Sina. Hermann Boerhave (16668-1738) proposed that sepsis was a result of toxic substances in the air. Justus Von Liebig said sepsis was due to contact between wound and oxygen. Ignaz Semmelweis (1818-1865)

developed modern view of sepsis. His development of modern concept of sepsis was based on death of many women from puerperal sepsis and he identified lack of antisepstic measures used by medical students during examination as the cause. He brought the concept of hand washing by chlorinated lime before doing gynaec examination.

Louis Pasteur, the French chemist proposed that bacteria or microbes cause disease. He brought the concept of sterilisation of fluid by heating. Antiseptic techniques was introduced by Joseph Lister later. After developing antiseptic techniques he noticed mortality was reduced in patients post-amputation. Steam sterilisation was introduced by Robert Koch.

Germany physician H.Lennhartz initiated the new concept of sepsis as a bacterial disease from older concept of putrefaction. Hugo Scottmuller explained the modern definition of sepsis "Sepsis is present if a focus has developed from which pathogenic bacteria, constantly or periodically, invade the bloodstream in such a way that this causes subjective and objective symptoms".[8] He also proposed "A therapy should not be directed against bacteria in the blood but against the released bacterial toxins.[8] After development of antiseptic precautions also many people were dying due to sepsis and septic shock. Later antibiotics were introduced and death rate got reduced.

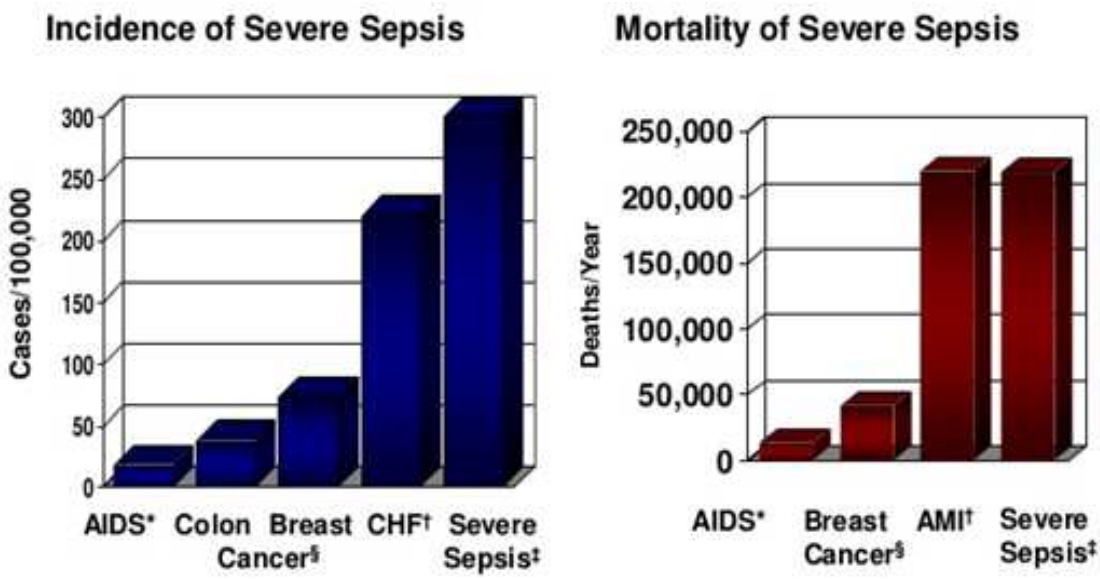
Asbough in the year 1967 found out patients admitted in IMCU Intensive medical care unit developed severe breathlessness, diffuse alveolar infiltration and reduced lung compliance. It was named as ARDS Acute respiratory distress syndrome. And later it was found out that ARDS was caused by inflammatory reaction in the body during sepsis. Finally Roger Bone proposed a sepsis definition that is still in use "Sepsis is defined as invasion of microorganisms and/or their toxins into the bloodstream, along with the organism's reaction against this invasion.[8]

INCIDENCE OF SEPSIS:

The annual global incidence of sepsis is around 13 million and mortality due to sepsis is around 4 million. Severe sepsis causes mortality of around 50%.Patients with diabetes with sepsis constitutes around 22% of total sepsis patients.[9] The global incidence as well as complications of sepsis is in continuously rising trend.

As a cause of mortality Sepsis ranks much higher than majority of other killer diseases. And it's illustrated in the below picture.

incidence of sepsis compared with incidence of other major diseases:



Angus DC et al Critical care medicine 2010
CHF - Congestive heart failure , AMI - Acute Myocardial Infarction

DEFINITIONS

Based on the consensus held among international experts, specific definitions of sepsis and other allied conditions have been formulated.

SIRS – Systemic inflammatory response syndrome is defined as presence of 2 or more following factors[10]

1) Temperature <36 or >38.3 degree Celsius

2) Respiratory rate >20

3) WBC count >12,000 or <4,000 or band forms more than 10%

4) Heart rate >90

Some experts also included two additional criteria .These are

1. Acute onset of altered sensorium

2. Increased plasma glucose

The term Infection refers to the presence of microbes in an otherwise normally sterile body fluid or cavity (for ex.Urinary tract) or the development of inflammatory response to microbes in the body fluid/cavity that normally carries micro organisms (for ex.GIT).

Sepsis may be defined as presence of two or more criteria of SIRS plus either proven or suspected infection.[12]

The diagnostic criteria of sepsis was later modified in the year 2001 in the international conference held by the American Thoracic society(ATS), American College Of Physicians (ACCP) , Society Of Critical Care Medicine(SCCM), Surgical Infection Society(SIS), European Society Of Intensive Care Medicine (ESICM).The new diagnostic criteria includes the following parameters given in the table.

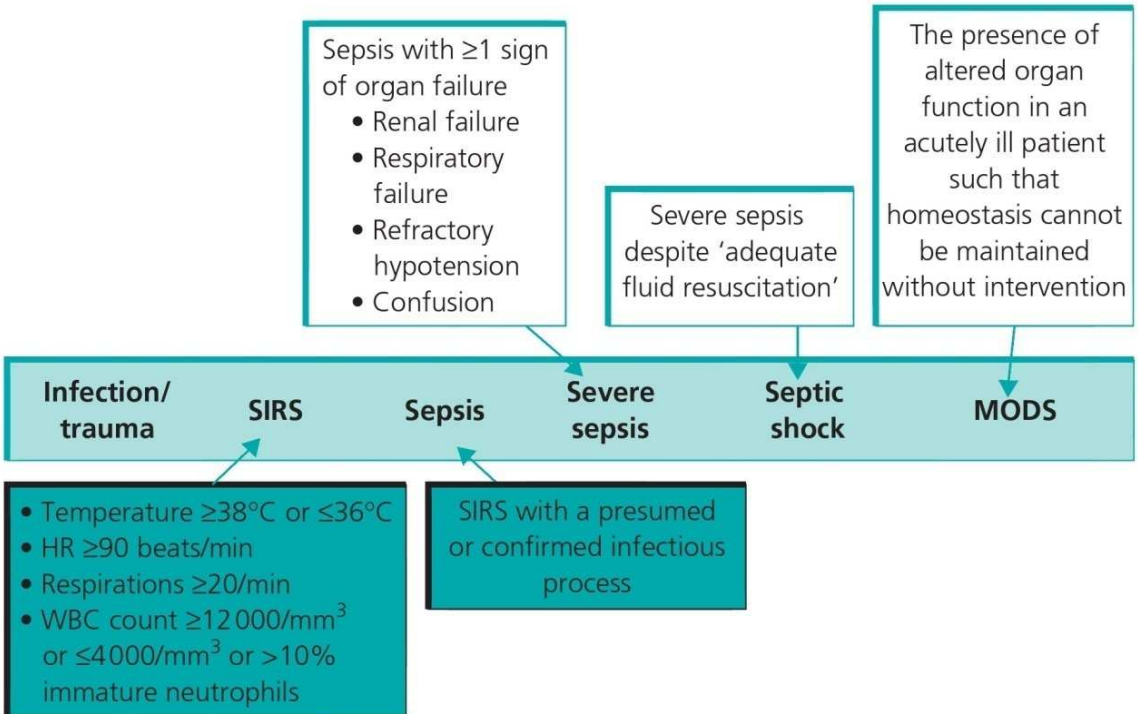
General parameters
Fever (core temperature >38.3°C)
Hypothermia (core temperature <36°C)
Heart rate >90/min or >2 SD above the normal value for age
Tachypnoea: >20/min
Altered mental status
Significant oedema or positive fluid balance (>20 ml/kg over 24 h)
Hyperglycaemia (plasma glucose >120 mg/dl or 6.7 mmol/l) in the absence of diabetes
Inflammatory parameters
Leukocytosis (white blood cell count >12 000/μl)
Leukopenia (white blood cell count <4000/μl)
Normal white blood cell count with >10% immature forms
Plasma C reactive protein >2 SD above normal value
Plasma calcitonin >2 SD above the normal value
Haemodynamic parameters
Arterial hypotension (SBP <90 mmHg, MAP <65 mmHg, or a decrease in SBP >40 mmHg in adults or <2 SD below normal for age)
Mixed venous oxygen saturation <65%
Central venous oxygen saturation <70%
Cardiac index >3.5 l/min
Organ dysfunction parameters
Arterial hypoxaemia (PaO_2/FiO_2 <300)
Acute oliguria (urine output <0.5 ml/kg/h for ≥2 h)
Creatinine >176.8 mmol/l
Coagulation abnormalities (INR >1.5 or aPTT >60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100 000/μl)
Hyperbilirubinemia (plasma total bilirubin >34.2 mmol/l)
Tissue perfusion parameters
Hyperlactataemia (>2 mmol/l)
Decreased capillary refill or mottling

Septic shock may be defined as symptoms and signs of severe sepsis plus extremely very low blood pressure that does not respond adequately to simple fluid replacement.[10]

MODS (Multiorgan dysfunction syndrome) is defined as presence of organ dysfunction in an acutely ill patient in a way that homeostasis cannot be maintained without intervention.[11] It is classified as primary and secondary. Primary MODS develops because of well defined direct insult and in this organ dysfunction occurs early and attributable directly to the insult itself. Secondary MODS develops as a result of host response and is in relation to the context of SIRS.[11]

Thus all the above entities are part of the continuous spectrum of sepsis.

THE SPECTRUM OF SEPSIS AND ASSOCIATED MORTALITY:



PATHOPHYSIOLOGY OF SEPSIS:

Sepsis is a systemic disease triggered by the excessive activation of innate immune system. The clinical picture is produced by the synergistic combination of multiple pathways. In sepsis there is systemic inflammation leading to organ dysfunction. Cardiovascular system followed by renal is most commonly affected. After the patient recovers organ dysfunction will get reversed.

INNATE IMMUNE SYSTEM:

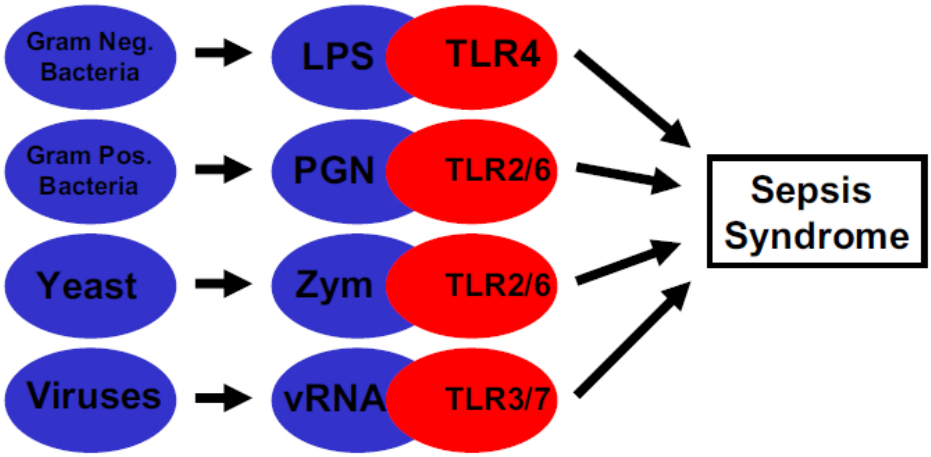
The innate immune system comprises of cellular (neutrophils, NK natural killer cell, dendritic cells, macrophages) and humoral components (coagulation system and complements).The innate immune system gets activated in early phase of sepsis. Its main function is to inhibit and prevent bacterial replication. After the micro organisms enter the body, it stimulates the innate immune system via the toll like receptors TLRs.

CELLULAR RESPONSE TO INFECTION:

The outer cell products of bacteria(both gram positive and gram negative) which are called Pathogen Associated Molecular Patterns (PAMP) binds to toll like receptors and initiate the bacterial sepsis. The

PAMPs usually comprised of peptidoglycans in gram positive organisms and lipopolysaccharides (LPS) in gram negative organisms.CD14 is needed for this binding process.

INTERACTION BETWEEN TLR AND PAMPS:



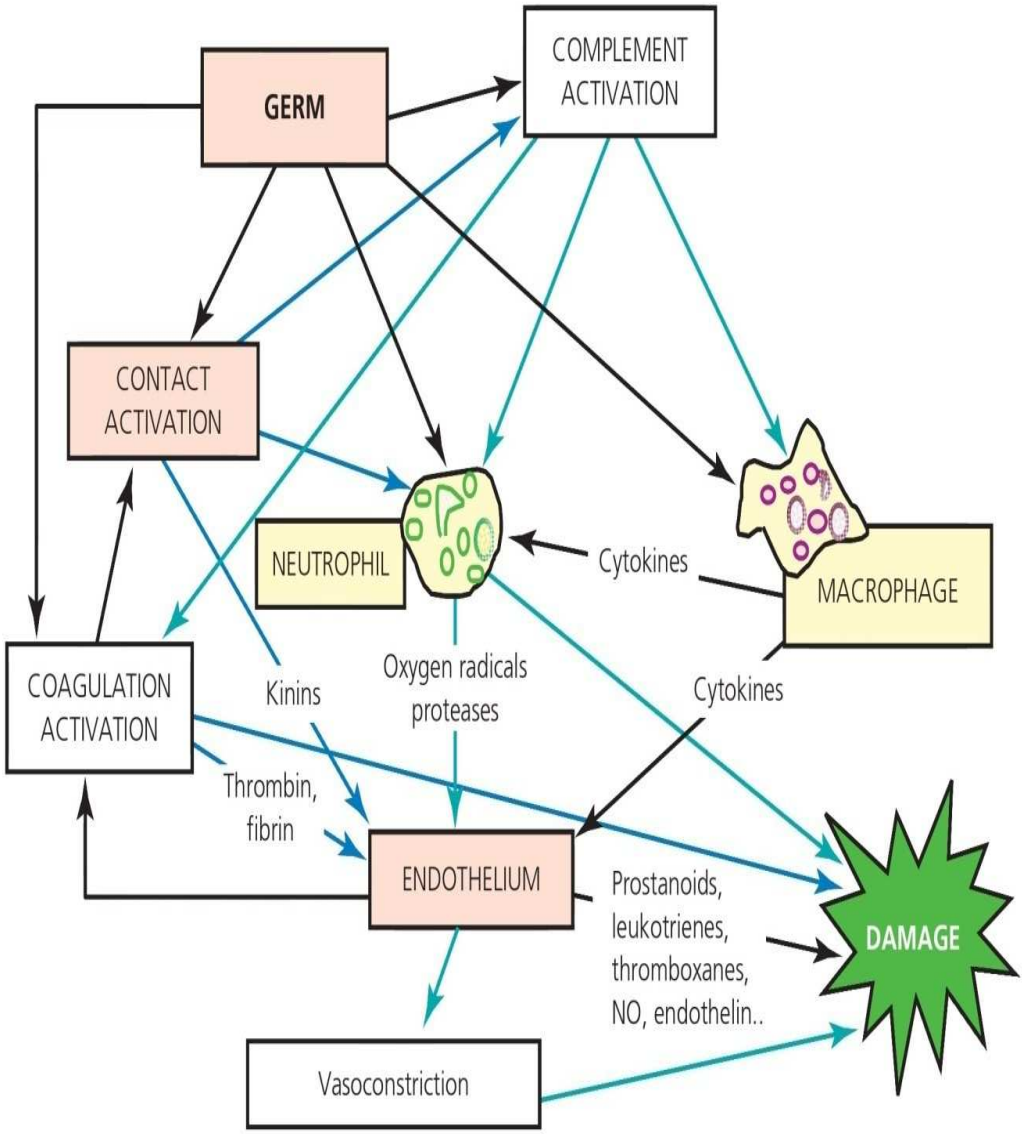
There are more than 10 TLRs identified in humans and all these are transmembrane proteins and they have intracellular domain which gets bind to protein kinases after their activation. One of most important TLR is TLR 4 which gets bind to the LPS component of gram negative bacteria and plays a major role in gram negative septicaemia. The specificity of TLRs varies to different kinds of microbes. These are found on endothelial cells, macrophages and leucocytes. There are many endogenous substances in our body like hyaluronate, heat shock proteins, heparan sulphate, fibronectin, fibrinogen and certain polymeric sugars.

This is the reason for the development of SIRS without any infection like in pancreatitis.

TLR	Ligands
TLR1 (heterodimer with TLR2)	Triacylated lipopeptides, lipomannans from *Mycobacterium tuberculosis*
TLR2 (often dimer with TLR2 or 6)	Lipoproteins, peptidoglycans, lipoteichoic acids, yeast zymosan
TLR3	Double-stranded RNA
TLR4 (homodimer plus CD14 and MD2)	LPS, heat shock proteins, pneumolysin, respiratory syncytial virus coat proteins, heparan sulphate fragments, fibrinogen peptides
TLR5	Flagellin
TLR6 (heterodimer with TLR2)	Diacylated lipopeptides
TLR7	Responds to synthetic nucleosides and imidazoquinoline antivirals; native ligand is thought to be single-stranded RNA in endosomes
TLR8	Same as for TLR7
TLR9	Bacterial DNA—unmethylated CpG motifs
TLR10	Ligand unknown but TLR10 expressed in lung and B lymphocytes
TLR11	Uropathogenic bacteria in mice; absent in humans

There is liberation of proteases, nitric oxide, reactive oxygen species and pore-forming molecules after the activation of innate immune system which results in bacterial lysis. It also causes tissue dysfunction by destroying the patient's own cells.ex.NO causes sepsis induced mitochondrial dysfunction by inactivating circulating catecholamines. Many inflammatory mediators such as interleukins (1 & 6) and TNF-α are released by the innate immune system. And it also activates nearby immune cells.

PATHOGENESIS OF SEPSIS



ROLE OF VASCULAR ENDOTHELIUM

The vascular endothelium plays an important role in the pathogenesis of sepsis.[10] Bacteria and their products directly stimulate the vascular endothelium. The endothelial response depends on certain factors like Pts age, gender, comorbid conditions, genetic factors of the

host and also invading micro organisms. Endothelial function impairment causes morphological and functional changes which results in the following effects:

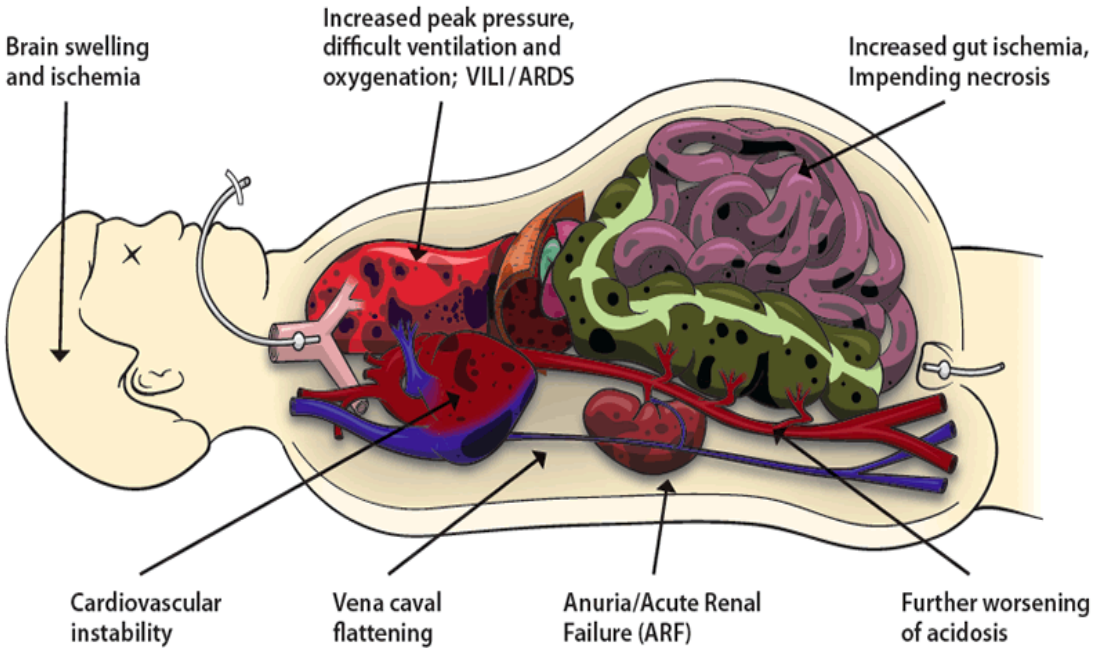
- Release of vasoactive substances like NO and prostacyclins in uncontrolled manner
- Adhesion and migration of WBCs
- Increased reactivity of the vascular smooth muscles in response to vasoconstrictors.
- Activation of platelets and also aggregation
- Loss of barrier function
- Raised pro apoptotic substances
- Imbalance between anti coagulants and pro coagulants.

Thus, finally sepsis occurs because of complex interaction between the microbial components and host function which includes both innate and acquired immunity and endothelial dysfunction.

ORGAN DYSFUNCTION IN SEVERE SEPSIS:

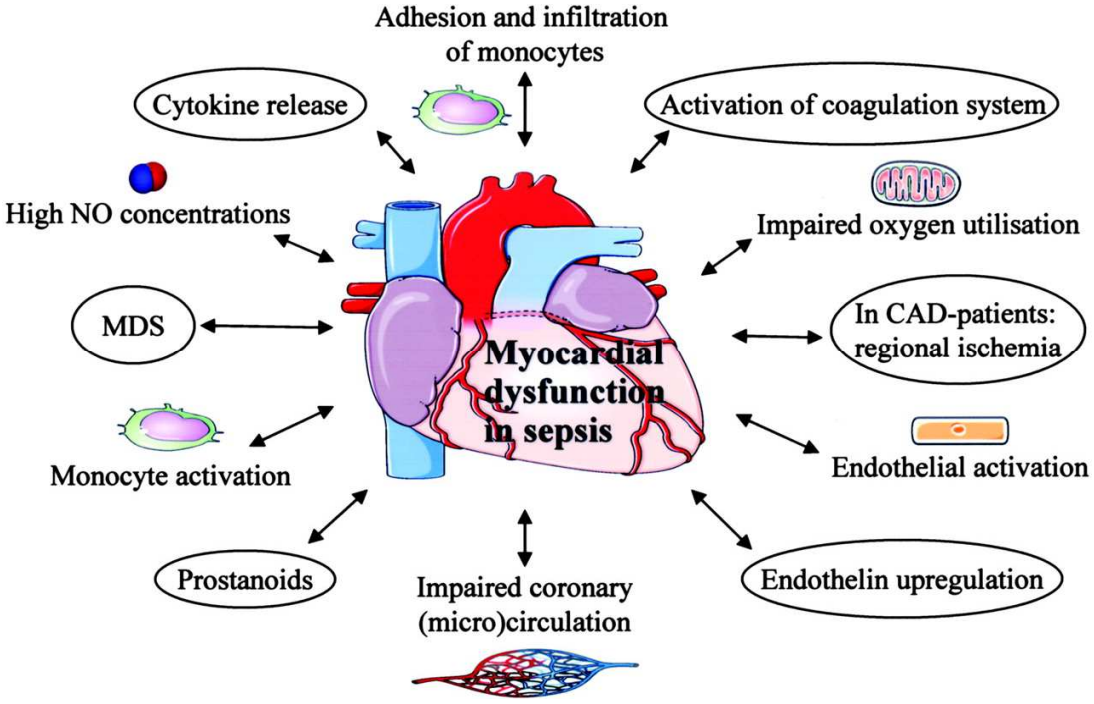
Sepsis causes damage to all the organs in the body including cardiovascular system, gastrointestinal system, central nervous system, coagulation pathways, renal, immune system and respiratory system. Dysfunction involving two or more organ systems is called MODS.

SEPSIS – MUTIORGAN FAILURE



CARDIOVASCULAR SYSTEM

Waisbren et al in the year 1951 first described the myocardial dysfunction in sepsis. In the early phase of sepsis there will be low systemic resistance which masks the reduced myocardial contractility. As sepsis progresses in the late phase, stroke volume and ejection fraction decreases.



RENAL SYSTEM

In 20% cases of sepsis, renal failure occurs. Sepsis is the most common cause of AKI-Acute Kidney Injury in critically ill patients. The normal diagnostic methods used to diagnose AKI like FENA- fractional excretion of sodium and urinary casts fails to detect sepsis related AKI. Many biomarkers like KIM 1- Kidney Injury Molecule, cystatin C, NGAL – Neutrophil Gelatinase Associated Lipocalin, urinary interleukin 18 helps to diagnose sepsis related AKI.

GASTROINTESTINAL SYSTEM:

Severe sepsis causes hypotension which causes reduction in perfusion pressure in the splanchnic circulation which results in liver dysfunction. There is endotoxemia due to bacterial translocation from the gut. Under normal conditions these toxins will be destroyed by the reticuloendothelial cells of the liver but in severe sepsis due to hepatic dysfunction, they directly enter the systemic circulation and causes inflammatory damage.

CENTRAL NERVOUS SYSTEM:

Severe sepsis causes septic encephalopathy and the patient can develop acute confusional state, delirium & coma.The factors responsible for development of septic encephalopathy are:

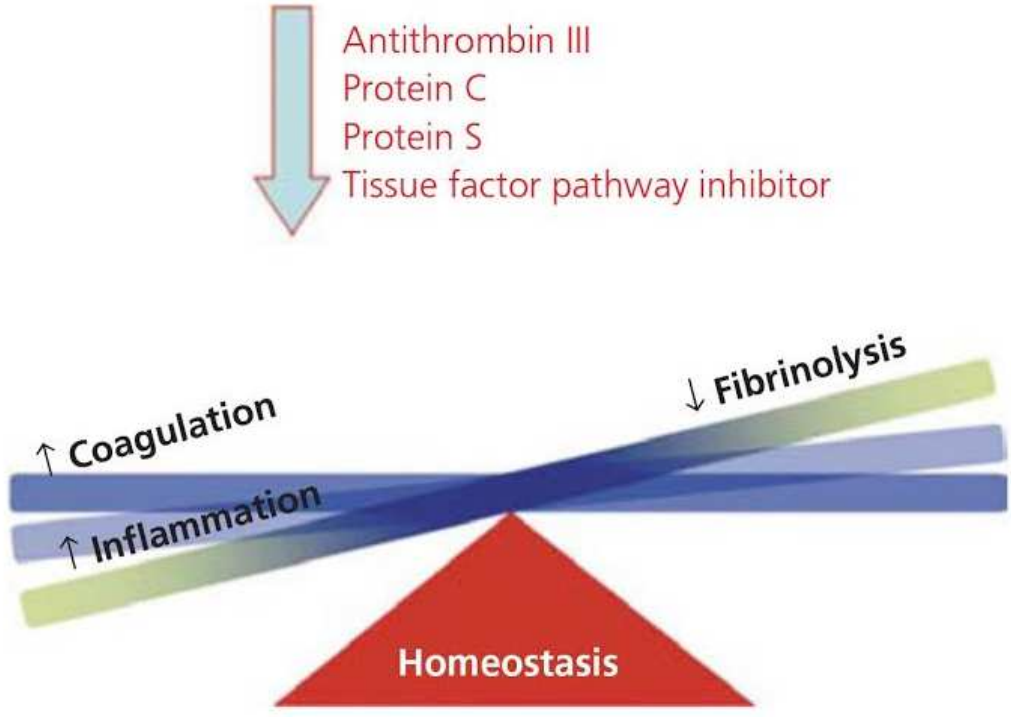
- Hypoxic encephalopathy
- Micro infarcts
- Blood brain barrier disruption
- Intracranial hemorrhage due to DIC
- Development of metastatic abscess
- Elevated cytokine levels

The septic encephalopathy results in residual long term neurological sequelae.

COAGULATION SYSTEM

Gram negative sepsis causes more damage to coagulation pathway because of endotheial dysfunction which results in DIC- disseminated intravascular coagulation.DIC will have both thrombotic and haemorrhagic manifestations. It also leads to the development of intracranial hemorrhage, infarcts, acute renal failure and microangiopathic haemolytic anemia (MAHA).

Severe sepsis causes imbalance between pro thrombotic and anti thrombotic factors as shown below.



CUTANEOUS MANIFESTATIONS

Sepsis causes skin lesions like vesicles, purpura, petechiae, necrosis and gangrene either directly or via disseminated intravascular coagulation. Micro thrombi cause disruption of blood vessels in the dermis. Meningococcus and Pneumococcus both causes purpura fulminans, cutaneous necrotic hemorrhagic lesion.

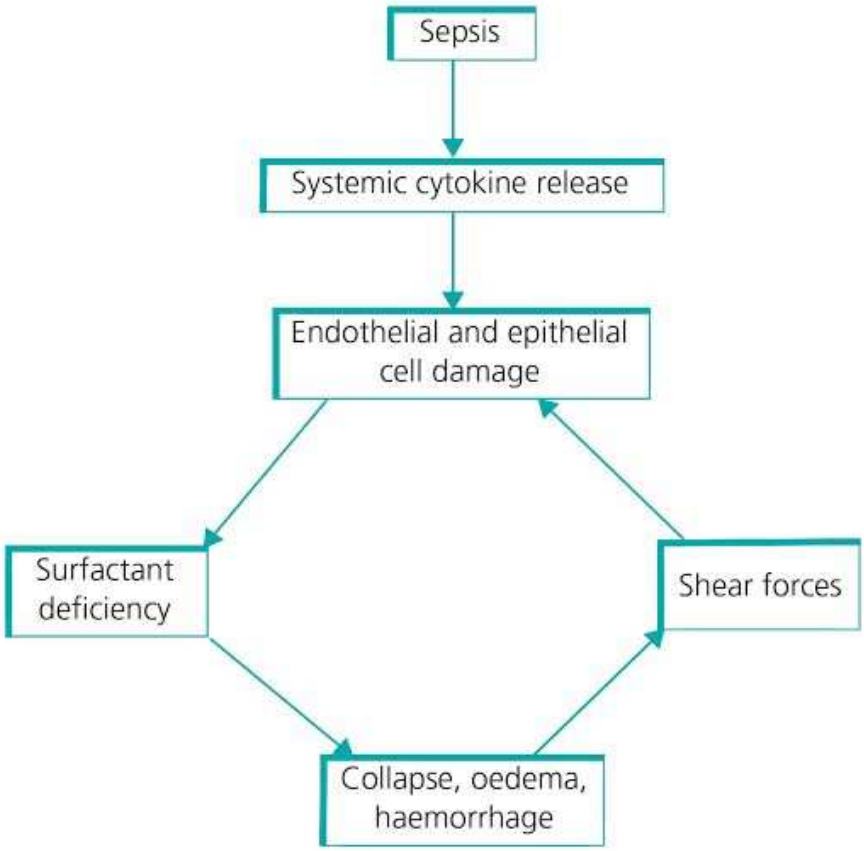
IMMUNE DYSFUNCTION:

Sepsis produces immunosuppressive state by dysregulating the immunological pathways via the cytokine storm.

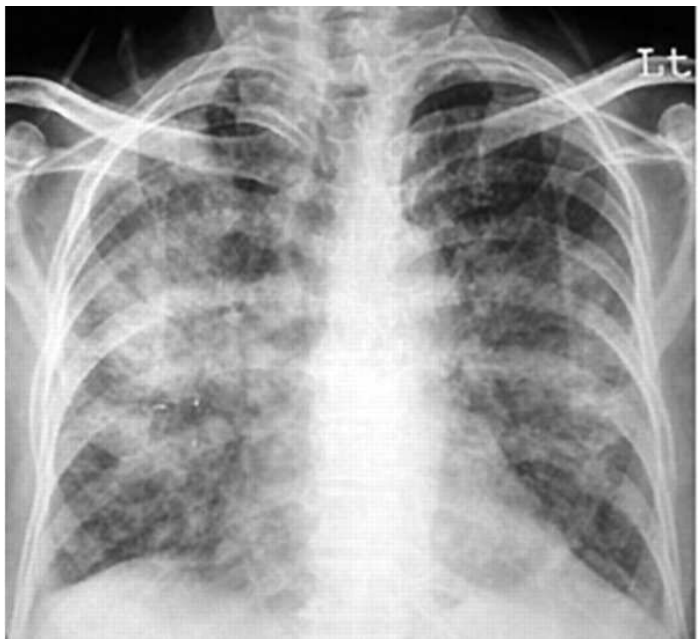
RESPIRATORY SYSTEM:

There is hyperventilation and respiratory alkalosis in the earliest stage of sepsis. Alveolar membrane disruption occurs due to alveolar and interstitial fluid accumulation plus inflammatory cells and cytokines. Type 1 pneumocytes is replaced by proliferation of type 2 cells with surfactant deficiency. Fluid accumulation in the interstitial space, development of alveolar exudates and fibrotic changes all leads to the condition called Acute Respiratory Distress Syndrome.

SEPSIS – ARDS PATHWAY



CHEST X RAY – ARDS

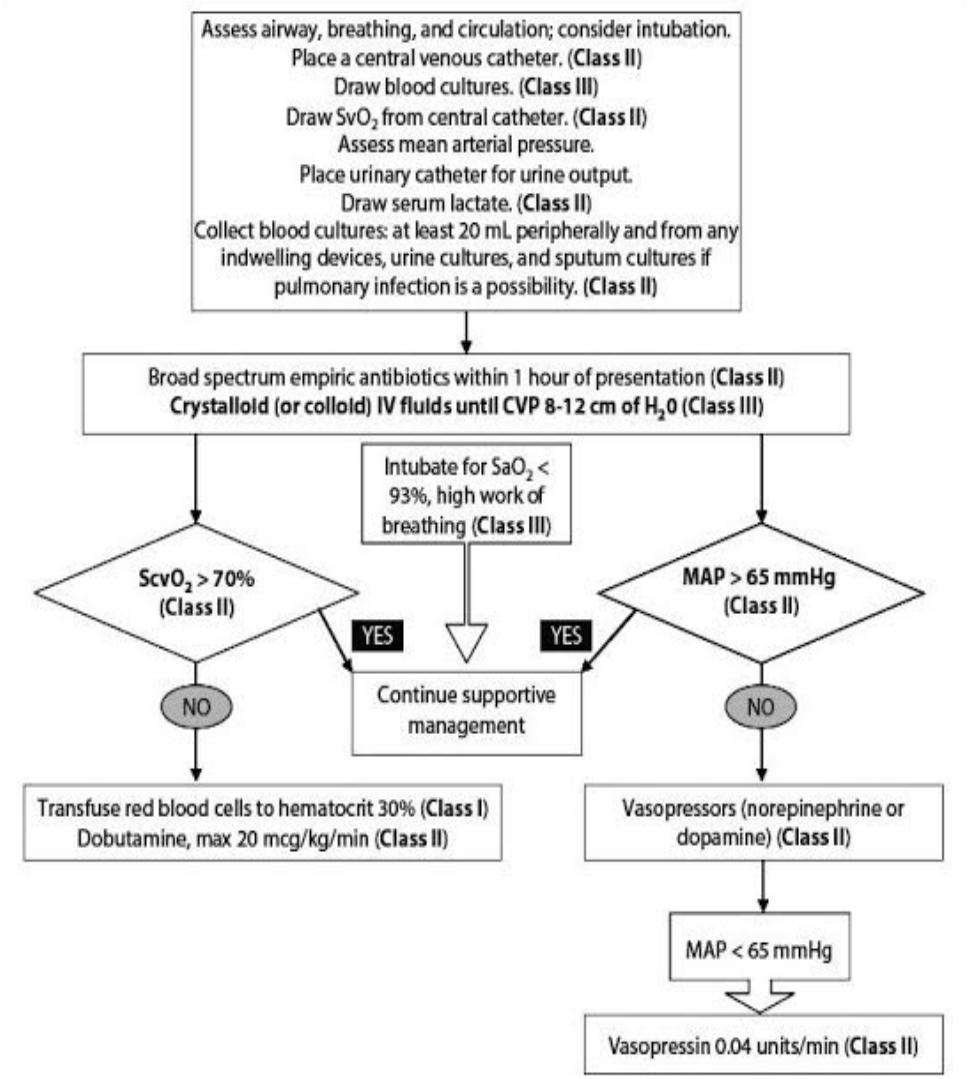


INVESTIGATIONS TO BE DONE IN SEPSIS:

1. Complete blood count – Leukocytosis or cytopenias indicate sepsis.
2. Liver function tests
3. Renal function tests
4. Coagulation profile
5. Arterial blood gas analysis(ABG)
6. Imaging (chest X ray ,X ray – paranasal sinuses, ultrasound abdomen ,CT and MRI imaging of relevant areas, echocardiography) to localise the source of infection
7. Cytokine and biomarker assays – if available
8. Blood cultures and cultures of relevant tissues or fluids ex.(sputum, urine, stool, CSF, pus, skin lesions, bone marrow). Blood cultures have to be taken from two or three different venepuncture sites
9. Microscopic examination of infected tissues/fluids and staining with gram stain/AFB
10. Molecular assays like PCR-polymerase chain reaction
11. Acute phase reactants like C Reactive Protein (CRP), procalcitonin and the erythrocyte sedimentation rate (ESR) – these helps in assessing the severity of infection
12. Serum cortisol and ACTH – to diagnose adrenal insufficiency associated with critical illness.

MANAGEMENT OF SEPSIS

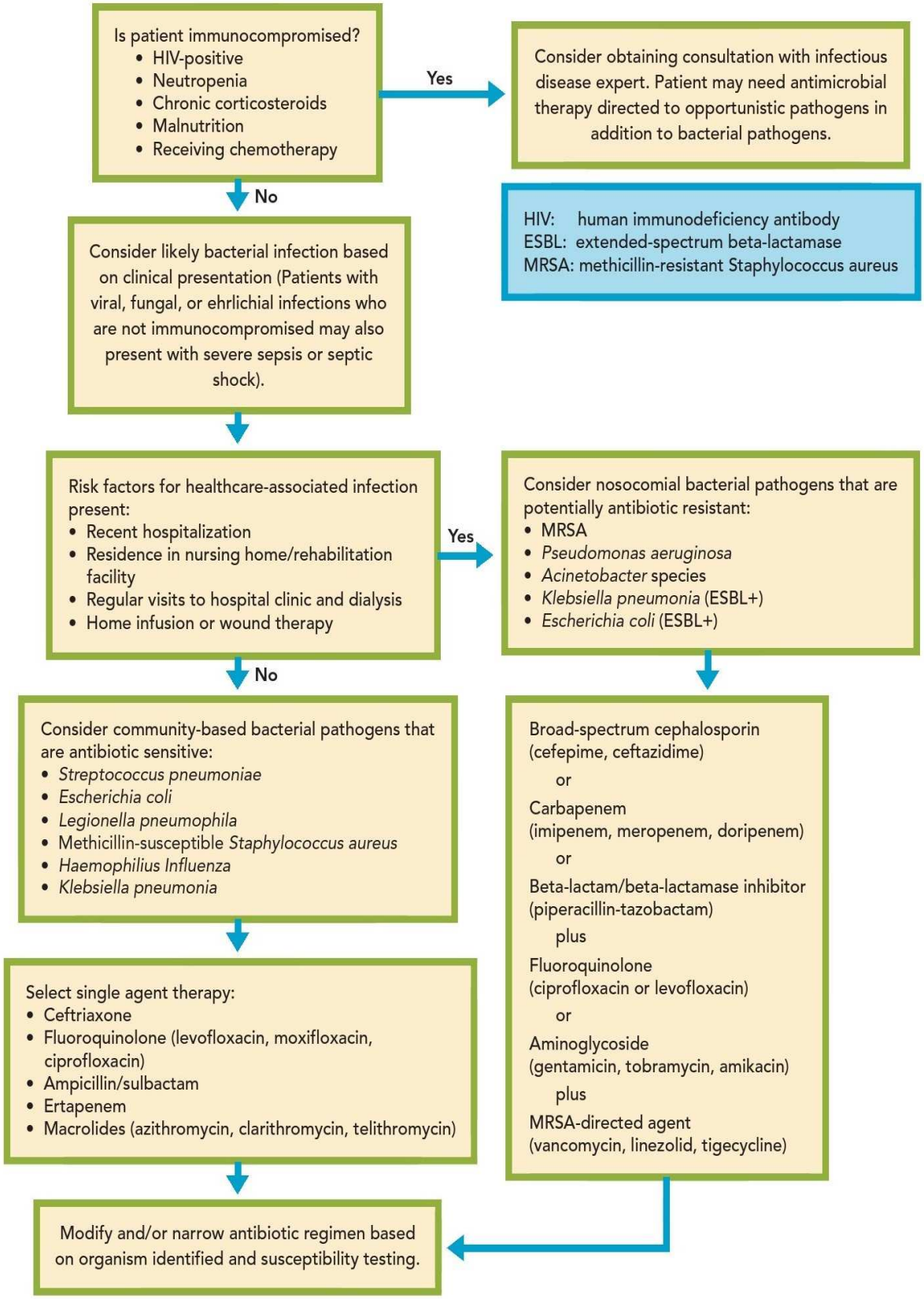
- **INITIALRESUSCITATION**



ANTIBIOTICS:

If a patient is suspected to have infection antibiotics are started empirically based on the site of infection and possible causative organisms. After the culture sensitivity report, appropriate antibiotics have to be given. Ideally antibiotics are recommended for a period of 7 – 14 days.

ALGORITHM FOR ANTIBIOTIC PROTOCOL IN SEPSIS:



- **NUTRITIONAL SUPPORT:**

Enteral feeding is recommended for all patients who are conscious and able to swallow foods without risk of aspiration. Ryles tube feeding is recommended for others. Adequate calories should be given by calculating based on the body weight.

- **SOURCE CONTROL:**

Source of infection has to be identified in all patients. Surgical management has to be considered for all closed space infection. Any long standing IV cannulas has to be removed.

Important drugs with their doses and effects used in the management of severe sepsis are listed below.

I. Vasopressors		CO	MAP	SVR
Norepinephrine	0.05–0.5 μg/kg/min	–/+	++	+++
Dopamine	5–20 μg/kg/min	++	+	++
Epinephrine	0.05–2 μg/kg/min	++	++	+++
Phenylephrine	2–10 μg/kg/min	0	++	+++
Vasopressin	0.04 units/min	0	+++	+++
II. Inotrope				
Dobutamine	2.5–10 μg/kg/min	+++	–/+	–/0
III. Drotrecogin alfa (activated)	24 μg/kg/hr for 96 hr			
IV. Corticosteroids				
Hydrocortisone (+/– fludrocortisone 50 μg daily)	50 mg every 6 hr			

Key : CO-cardiac output , MAP – mean arterial pressure ,
SVR – systemic venous return

- **GLYCEMIC STATUS:**

  Blood sugar level should be maintained <180 mg/dl for control of sepsis.

- **ROLE OF STEROIDS:**

  Steroid is recommended for patients with septic shock unresponsive to IV fluids and vasopressors.

- **MANAGEMENT OF ARDS:**

  ARDS is managed with mechanical ventilation ideally with low tidal volume 6ml/kg and high PEEP to prevent alveolar collapse.

- **DIALYSIS:**

  Sepsis related AKI has to be treated with dialysis

- **DVT PROPHYLAXIS:**

  All patients who are immobilised has to be given dvt prophylaxis either pharmacological drugs like heparin or low molecular weight heparin or mechanical devices like compression stockings, intermittent pneumatic compression devices.

- **STRESS ULCER PREVENTION:**

  Proton pump inhibitors are preferred to histamine receptor

  blockers.

MONITORING THE ORGAN FUNCTION

Organ system	Parameter
Respiratory system	PaO2/FiO2 ratio
Renal system	Urine output and serum creatinine
Hematologic system	Platelet count
Central nervous system	Glasgow coma score
Hepatobiliary system	Serum bilirubin and liver enzymes
Cardiovascular system	Blood pressure, arterial lactate
Gastrointestinal system	Gastric intramucosal pH (pHi), ileus, blood in nasogastric aspirate

RISK PROGNOSTICATION IN SEPSIS

There are many scoring systems in practice to assess the severity, prognosis and also risk of hospital mortality in critically ill patients. Some of these scores are

- APACHE II { Acute Physiology and Chronic Health Evaluation } Score
- SAPS { Simplified Acute Physiology } Score
- SOFA {Serial Organ Failure Assessment } Score
- MPM { Mortality Prediction Model}

APACHE II SCORE

The APACHE II or the Acute Physiology and Chronic Health Evaluation Score was first developed by the US researchers led by Knaus et al. The model has been upgraded thrice following British and Irish studies and thus APACHE I, II and III are available. Of these the APACHE II, widely used has the advantages of simplicity and effectiveness. This score ranges from 0 to 71. It includes weightage for age, acute physiological parameters, past comorbid conditions and the following 12 parameters has to be taken within the first 24 hours of admission.

- Temperature
- Respiratory rate
- Heart rate
- Mean arterial pressure
- paO2
- arterial pH or serum bicarbonate
- serum sodium
- serum potassium
- serum creatinine
- Glasgow coma scale
- white blood cell count
- hematocrit

Physiologic Variable	High Abnormal Range					Low Abnormal Range				
	+4	+3	+2	+1	0	+1	+2	+3	+4	Points
Temperature - rectal (°C)	≥41°	39 to 40.9°		38.5 to 38.9°	36 to 38.4°	34 to 35.9°	32 to 33.9°	30 to 31.9°	≤29.9°	
Mean Arterial Pressure - mm Hg	≥160	130 to 159	110 to 129		70 to 109		50 to 69		≤49	
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤39	
Respiratory Rate (non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5	
Oxygenation: A-aDO2 **or** PaO2 (mm Hg) a. FIO2 ≥0.5 record A-aDO2 b. FIO2 <0.5 record PaO2	≥500	350 to 499	200 to 349		<200 PO2>70	 PO2 61 to 70		 PO2 55 to 60	 PO2<55	
Arterial pH (preferred) Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABGs)	≥7.7 ≥52	7.6 to 7.69 41 to 51.9		7.5 to 7.59 32 to 40.9	7.33 to 7.49 22 to 31.9		7.25 to 7.32 18 to 21.9	7.15 to 7.24 15 to 17.9	<7.15 <15	
Serum Sodium (mEq/l)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	≤110	
Serum Potassium (mEq/l)	≥7	6 to 6.9		5.5 to 5.9	3.5 to 5.4	3 to 3.4	2.5 to 2.9		<2.5	
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6			
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20	
White Blood Count (total/mm3) (in 1000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1	
Glasgow Coma Score (GCS) Score = 15 minus actual GCS										
A. Total Acute Physiology Score (sum of 12 above points)										
B. Age points (years) ≤44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6										
C. Chronic Health Points (see below)										
Total APACHE II Score (add together the points from A+B+C)										

SOFA SCORE:

It's used to monitor the functioning of the organ systems in a critically ill patient.[13] The following 6 organ systems are used in the calculation of the score.

- Cardiovascular system
- Respiratory system
- Liver
- Renal system
- Central nervous system
- Coagulation

The score ranges from 0 to 24.It can be calculated serially and rise in the score in the first 24 to 48 hrs indicate increased risk of mortality.

SOFA SCORE CALCULATION CHART

Score points	1	2	3	4
Respiration				
PaO_2/FiO_2	<400	<300	<200	<100
			with respiratory support	with respiratory support
Cardiovascular				
Hypotension*	MAP <70 mmHg	Dopamine ≤5 or	Dopamine >5 or	Dopamine >15 or
		dobutamine in any dose	epinephrine ≤0.1 or	epinephrine >0.1 or
			norepinephrine ≤0.1	norepinephrine >0.1
Liver				
Bilirubin mg/dl	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Renal				
Creatinine mg/dl	1.2–1.9	2.0–3.4	3.5–4.9	5.0
or urine output			or <500ml/2 4h	or <200ml/24 h
Coagulation				
Platelets $\times 10^3/mm^3$	< 150	< 100	< 50	< 25
Central nervous system				
Glasgow Coma Scale	13–14	10–12	6–9	< 6

* Adrenergic agents administered for at least 1 h (doses are given in µg/kg/min)

MATERIALS AND METHODS

MATERIALS AND METHODS

Study Centre

Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai

Duration of the Study

6 months

Study Design

Observational study

Sample Size

100 patients

Inclusion criteria

All adult patients > 18 yrs with previously established or newly diagnosed type 2 diabetes admitted to medical wards with sepsis[2]

Exclusion Criteria

1. Chronic renal failure

2. End stage malignant disease

3. Immunosuppressive therapy

4. Type 1 diabetes mellitus

5. Pregnancy

6. Decompensated liver disease

7. Anaemia (all types)

Methodology (Materials and Methods)

Patients selected according to inclusion and exclusion criteria will be subjected to following steps:

1. History

2. Clinical examination

3. HbA1c on the day of admission

4. Correlating HbA1c with other parameters like blood glucose, CRP, APACHEII, SOFA score on the day of admission

5. To look for outcome of patients after 30 days

Data Collection and Methods

Patients will have their history taken according to a Questionnaire and will be subjected to clinical examination

Analysis Plan

SPSS, Epi INFO

Sponsorship (Yes/ No)

No

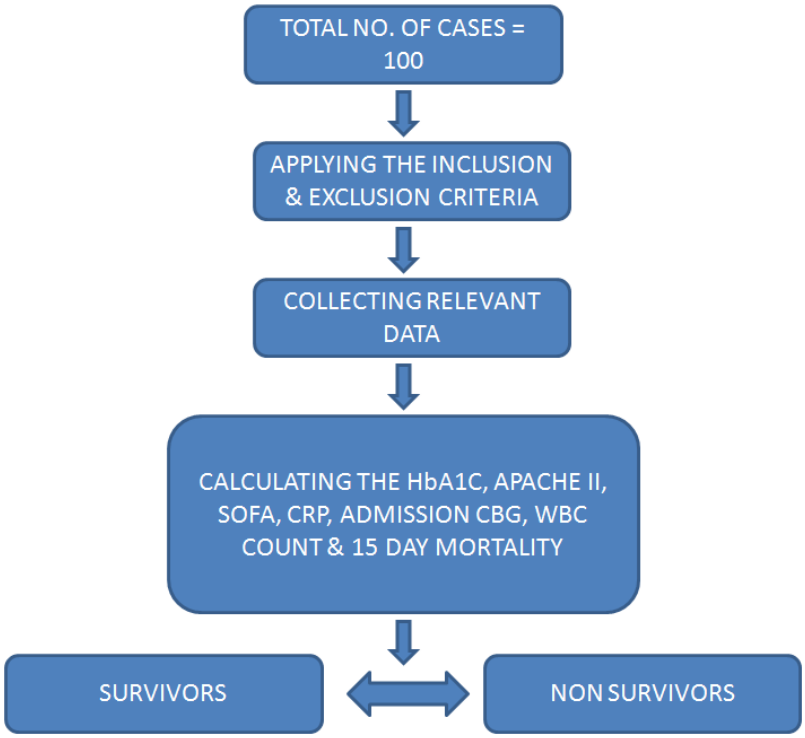
Conflict of Interest

No

OBSERVATIONS AND RESULTS

OBSERVATIONS AND RESULTS

FLOW CHART OF THE METHODOLOGY



30 DAYS MORTALITY RATES IN TYPE 2 DIABETES PATIENTS WITH SEPSIS

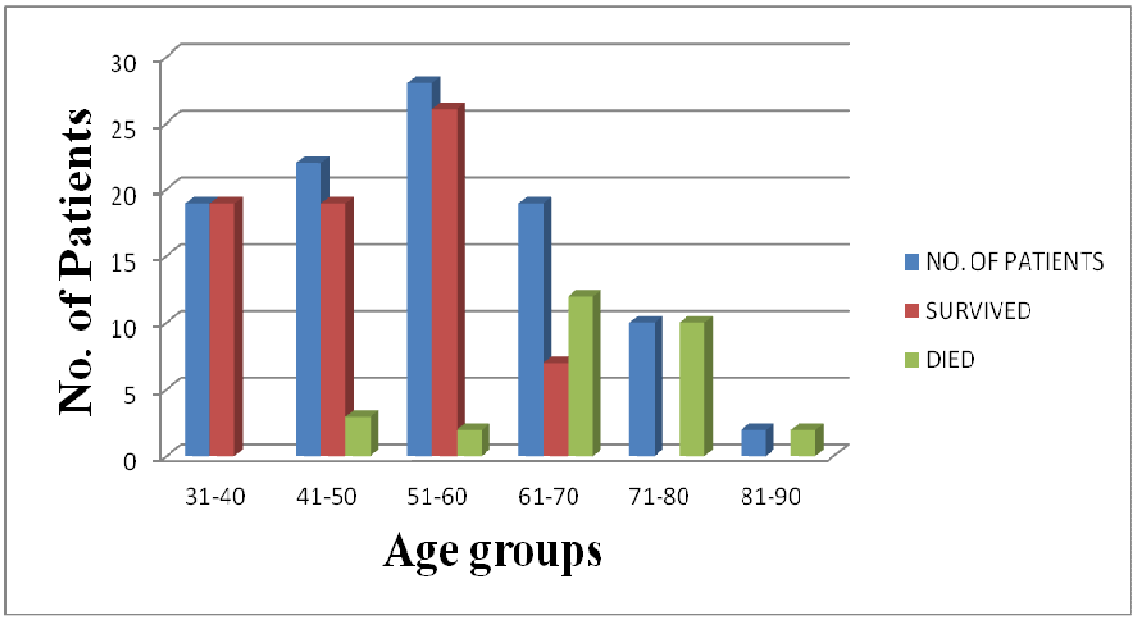
	NUMBER OF PATIENTS	PERCENTAGE
SURVIVED	71	71%
DIED	29	29%
TOTAL	100	100%

In our study the mortality rate in type 2 diabetes patients with sepsis was found to be 29% which is consistent with other studies.

AGEWISE DISTRIBUTION OF SURVIVORS AND NON SURVIVORS

AGE GROUP	NO. OF PATIENTS	SURVIVED	DIED	MORTALITY %
31-40	19	19		0%
41-50	22	19	3	14%
51-60	28	26	2	7%
61-70	19	7	12	63%
71-80	10		10	100%
81-90	2		2	100%

The majority of deaths were in patients aged above 60 years



AGE AS A RISK FACTOR FOR MORTALITY IN TYPE 2 DIABETES IN SEPSIS

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
AGE	48	9.58	67	9.32	<0.001**

The p value being <0.001 indicates that in our study, the age difference between the survivor group and non survivor group was highly significant

SEX WISE DISTRIBUTION OF SURVIVORS AND NON SURVIVORS

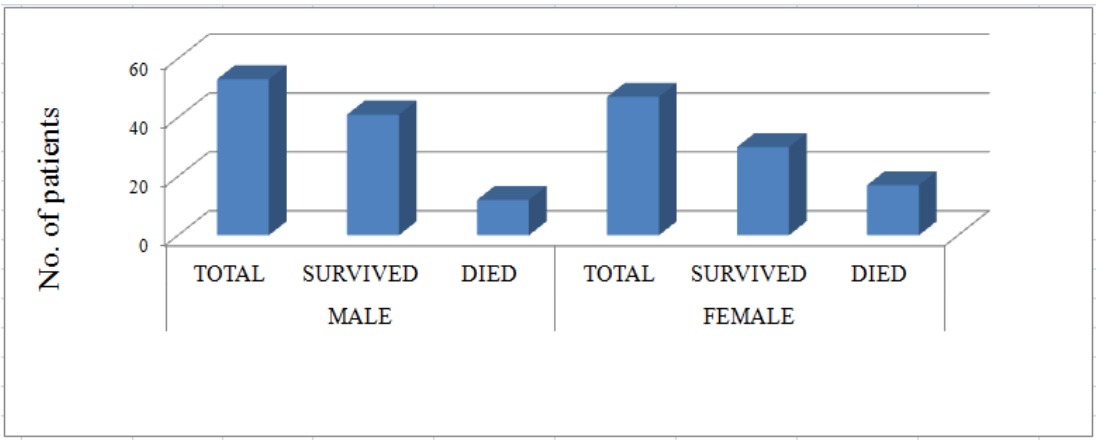
MALE			FEMALE		
TOTAL	**SURVIVED**	**DIED**	**TOTAL**	**SURVIVED**	**DIED**
53	41	12	47	30	17

Thus the mortality is noted to be

22.64% in males and

36.17% in females

The mortality rates appear to be higher in females than males.

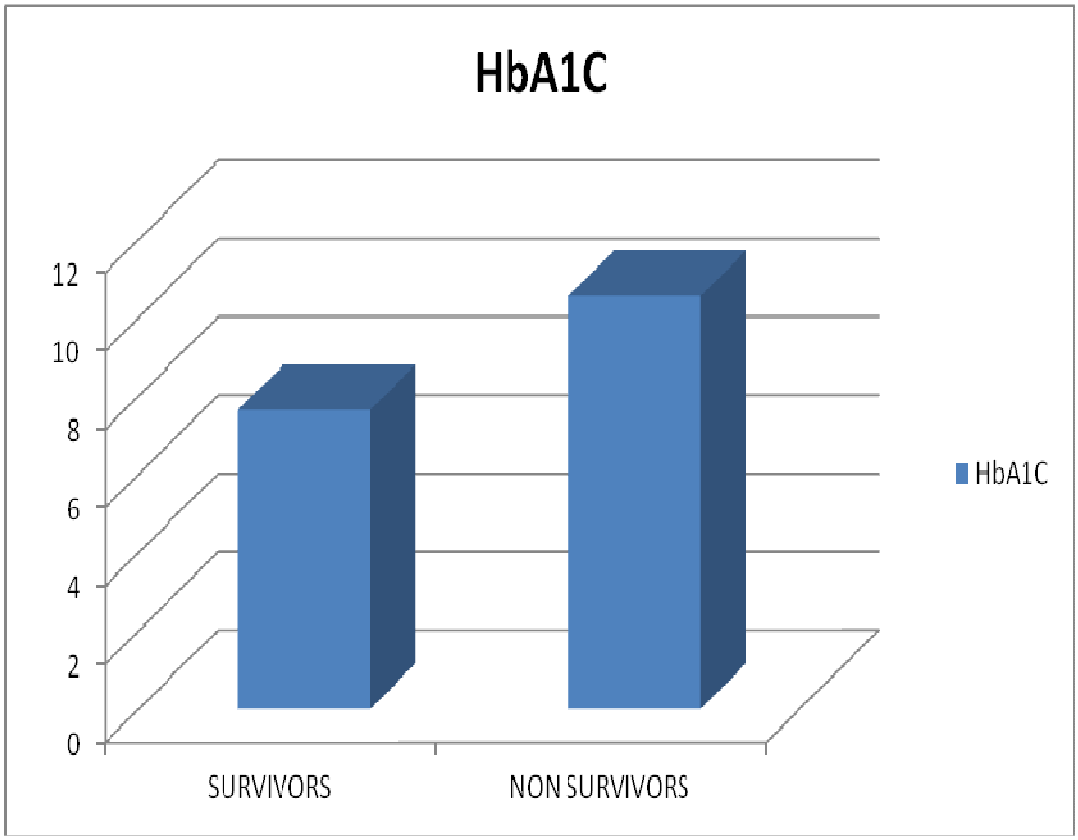


HbA1c AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
HbA1c	7.641	0.5987	10.552	1.2645	<0.001**

P value is highly significant, implying that HbA1c is a good predictor of 30 DAYS mortality in type 2 diabetes patients with sepsis

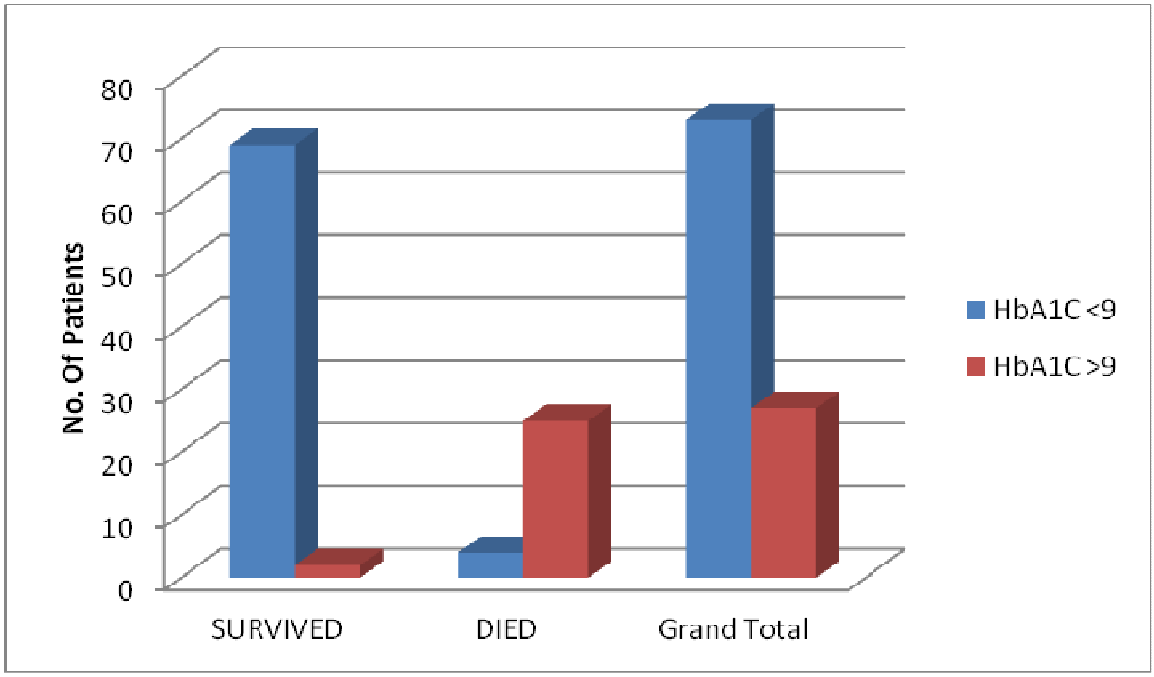
BAR DIAGRAM SHOWING THE CORRELATION BETWEEN HbA1c AND 30 DAYS MORTALITY



CORRELLATION BETWEEN HBA1C VALUE AND MORTALITY

	SURVIVED	DIED	TOTAL	MORTALITY %
HbA1c <9	69	4	73	5%
HbA1c >9	2	25	27	93%

It clearly shows that the mortality rate was found to be 93% in Patients with HbA1c value more than 9.

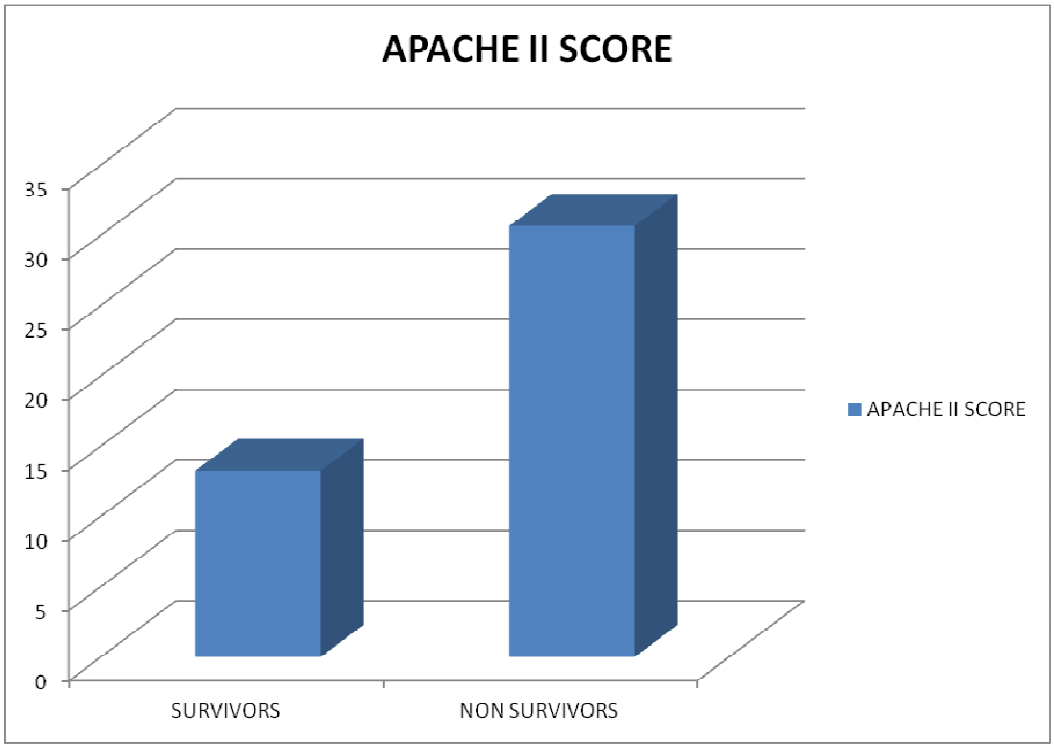


APACHE II SCORE AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
APACHE II SCORE	13.23	4.026	30.66	2.819	<0.001**

P value is highly significant, implying that APACHE II score (which is measured in the first 24 hours) is a good predictor of 30 DAYS mortality in type 2 diabetes patients with sepsis

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN APACHE II SCORE AND 30 DAYS MORTALITY

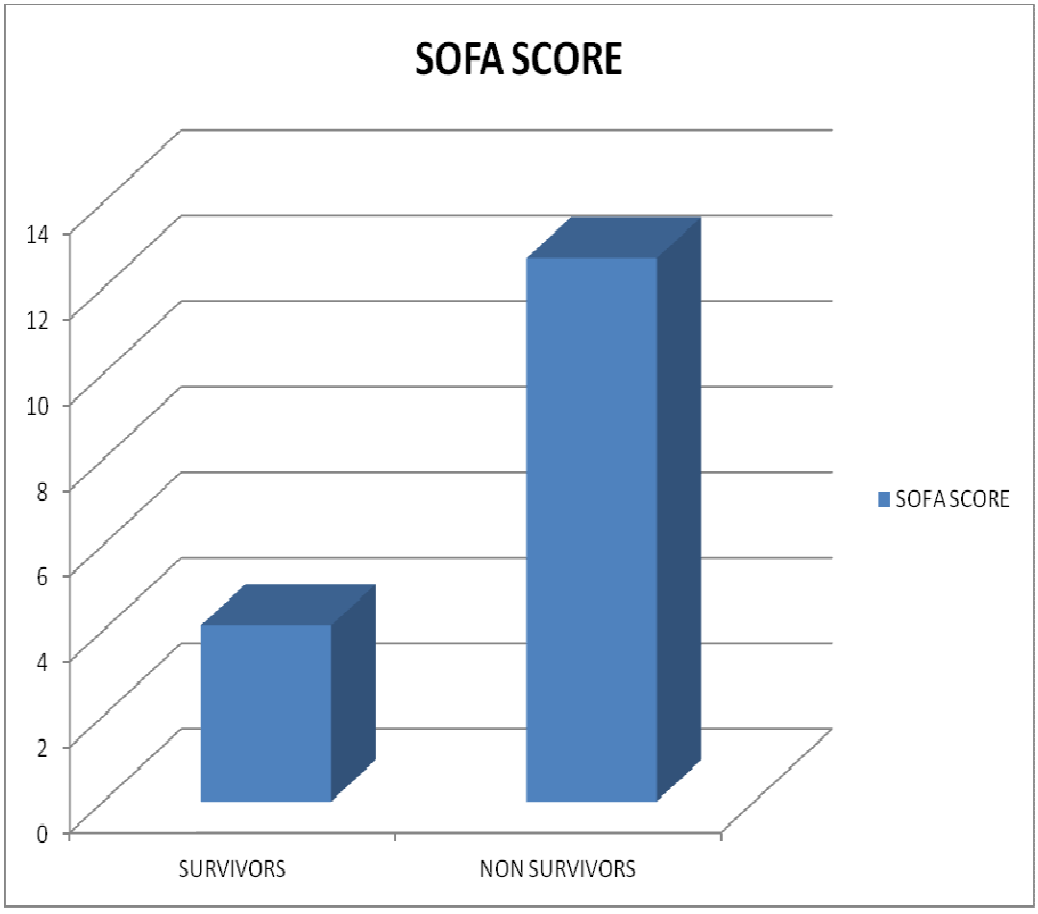


SOFA SCORE AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
SOFA SCORE	4.11	1.103	12.69	2.377	<0.001**

P value is highly significant, implying that SOFA score (which is measured in the first 24 hours) is a good predictor of 30 DAYS mortality in type 2 diabetes patients with sepsis

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN SOFA SCORE AND 30 DAYS MORTALITY

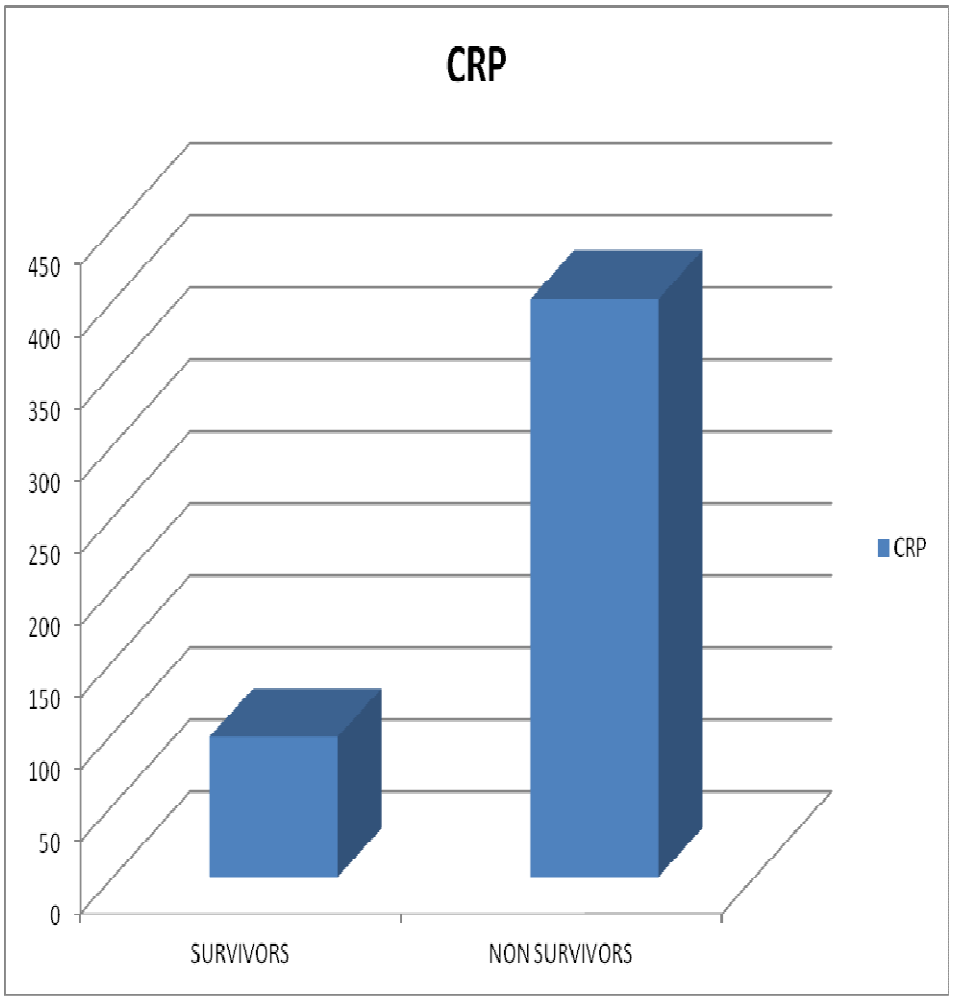


CRP AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
CRP	97.25	59.819	401.03	134.754	0.03

P value is significant, implying that CRP (which is measured in the first 24 hours) is a good predictor of 30 DAYS mortality in type 2 diabetes patients with sepsis

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN CRP AND 30 DAYS MORTALITY

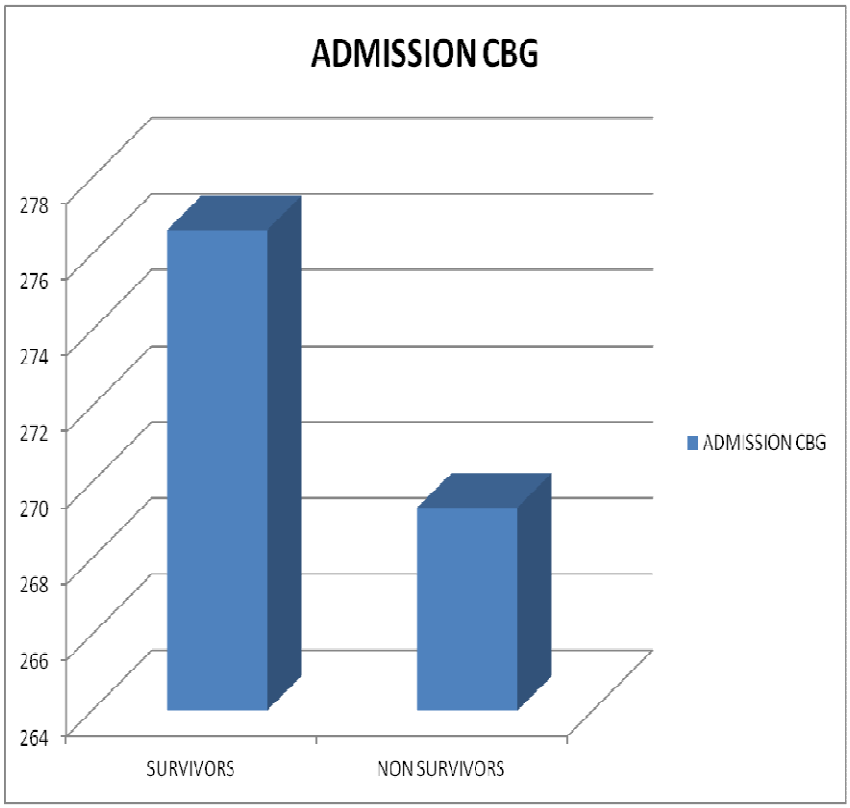


ADMISSION CBG AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
ADMISSION CBG	276.63	114.138	269.34	71.745	0.751

Here P value is greater than 0.05, indicating that admission CBG is not the predictor of mortality in type 2 diabetes patients admitted with sepsis

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN ADMISSION CBG AND 30 DAYS MORTALITY

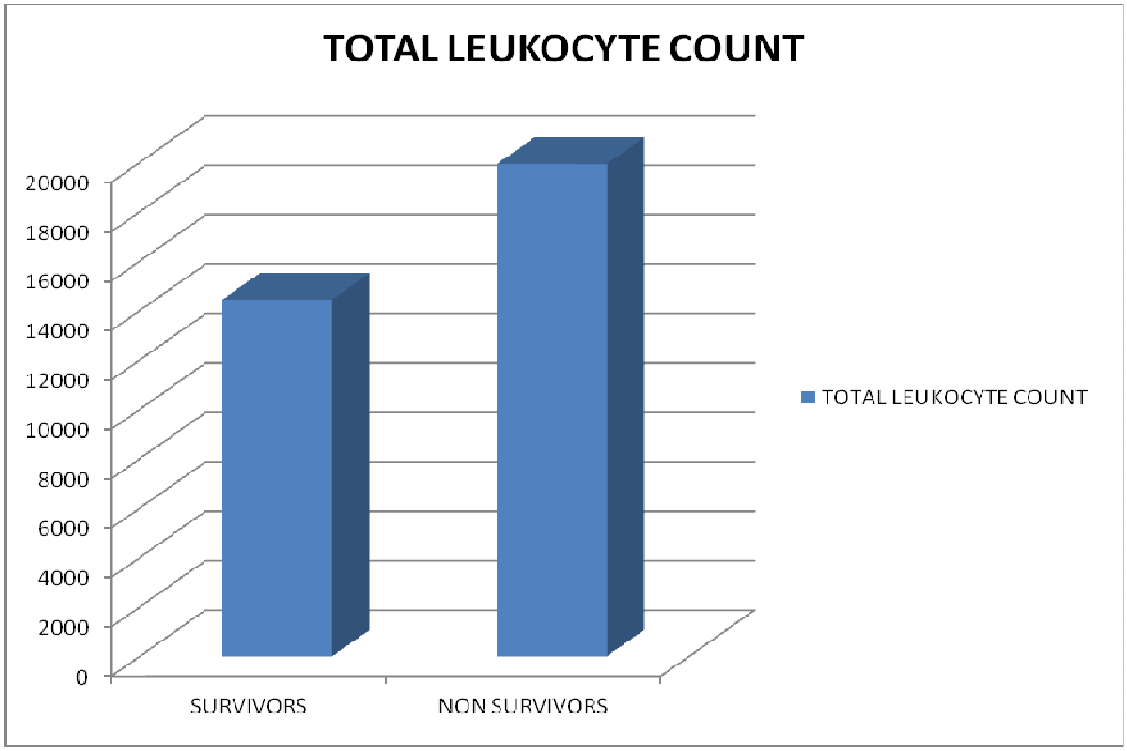


TOTAL LEUKOCYTE COUNT AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
TOTAL LEUKOCYTE COUNT	14440.35	3308.152	19932.38	6218.464	0.04

P value is significant, implying that total leukocyte count (which is measured in the first 24 hours) is a good predictor of 30 DAYS mortality in type 2 diabetes patients with sepsis

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN TOTAL LEUKOCYTE COUNT AND 30 DAYS MORTALITY

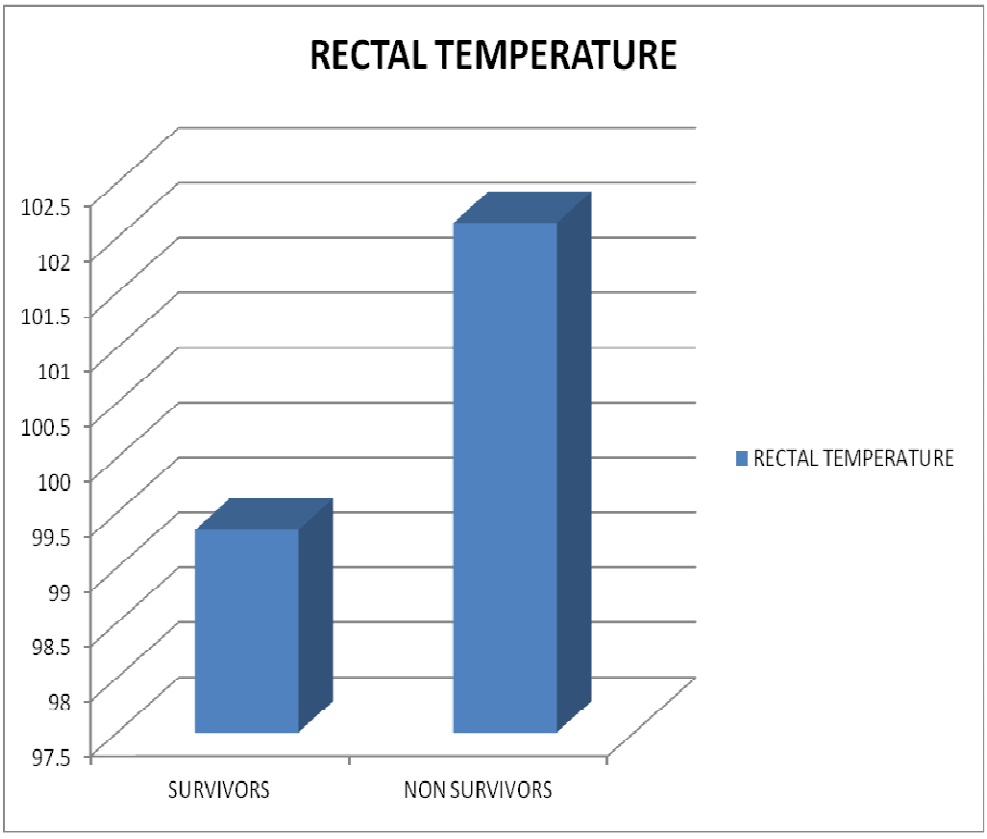


RECTAL TEMPERATURE AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
RECTAL TEMPERATURE	99.342	1.3963	102.134	1.8490	<0.001**

P value is highly significant, implying that rectal temperature is a good predictor of 30 DAYS mortality in type 2 diabetes patients with sepsis

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN RECTAL TEMPERATURE AND 30 DAYS MORTALITY

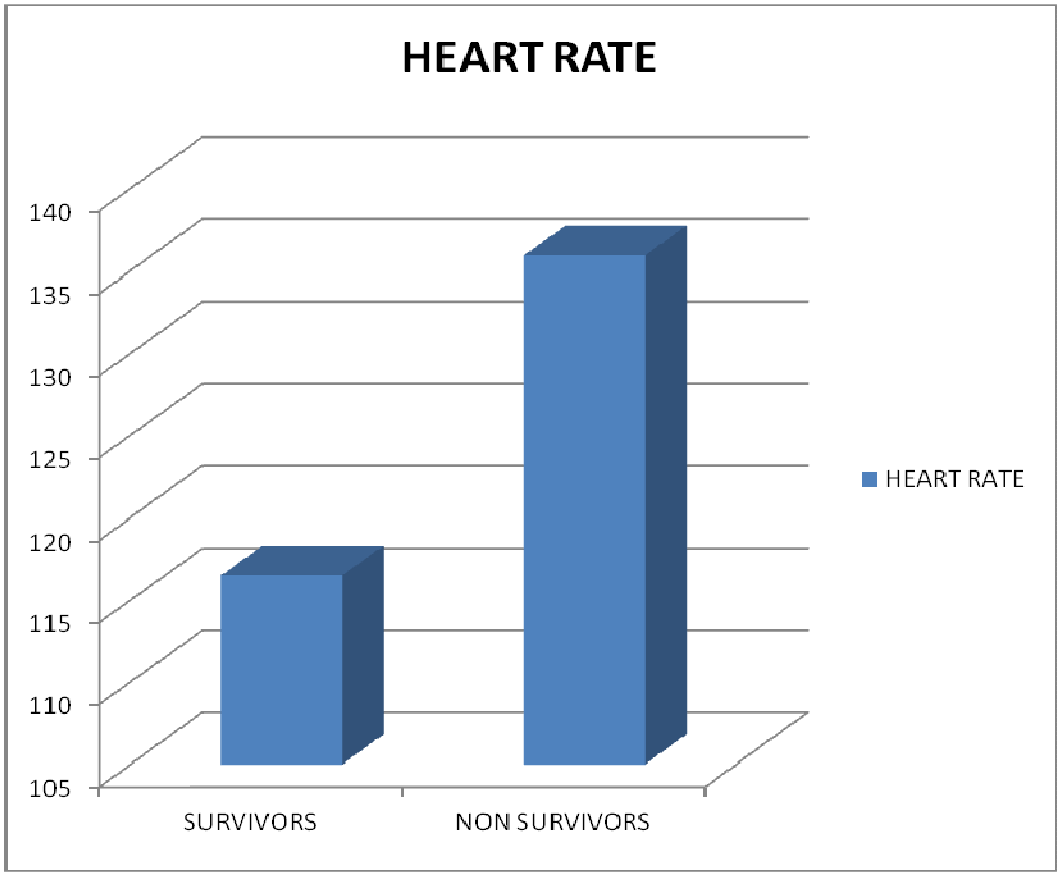


HEART RATE AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
HEART RATE	116.52	16.504	135.93	26.922	<0.001**

P value is highly significant, implying that heart rate is a good predictor of 30 DAYS mortality in type 2 diabetes patients with sepsis. The mean heart rate in survivors was 116 while that in non survivors was found to be higher - 135

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN HEART RATE AND 30 DAYS MORTALITY

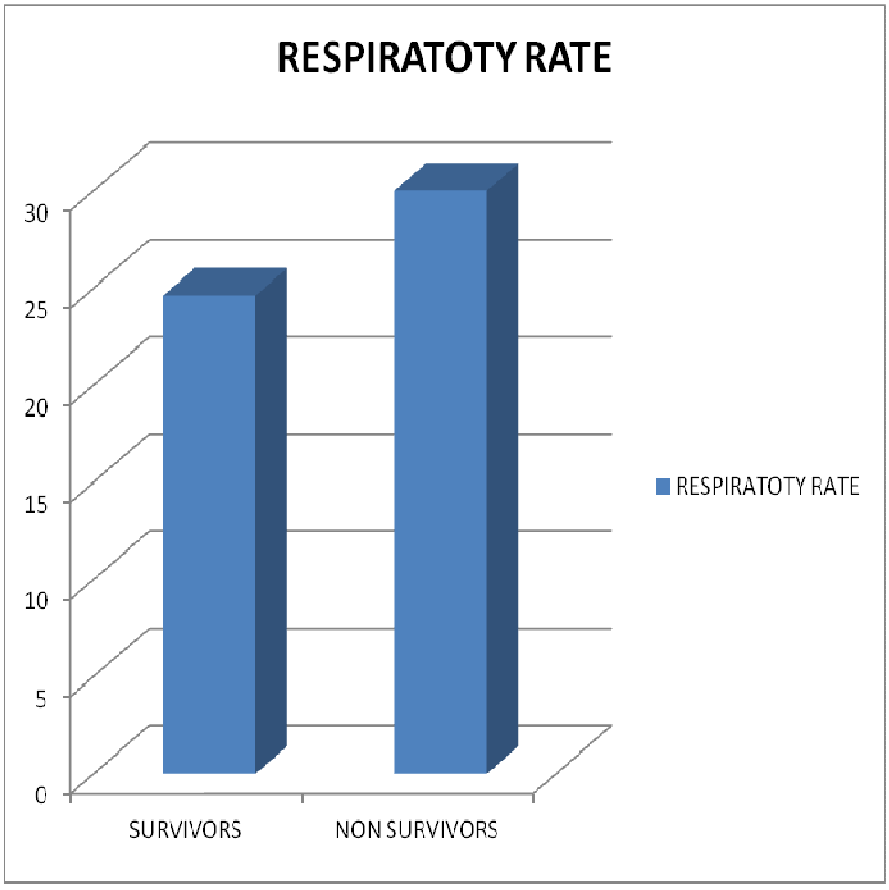


RESPIRATORY RATE AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
RESPIRATORY RATE	24.61	3.349	30.00	3.864	<0.001**

The mean respiratory rate in non survivors was found to be higher than the survivors and the P value is less than 0.001, suggesting that higher respiratory rate has an independent correlation with mortality in type 2 diabetes patients with sepsis

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN RESPIRATORY RATE AND 30 DAYS MORTALITY

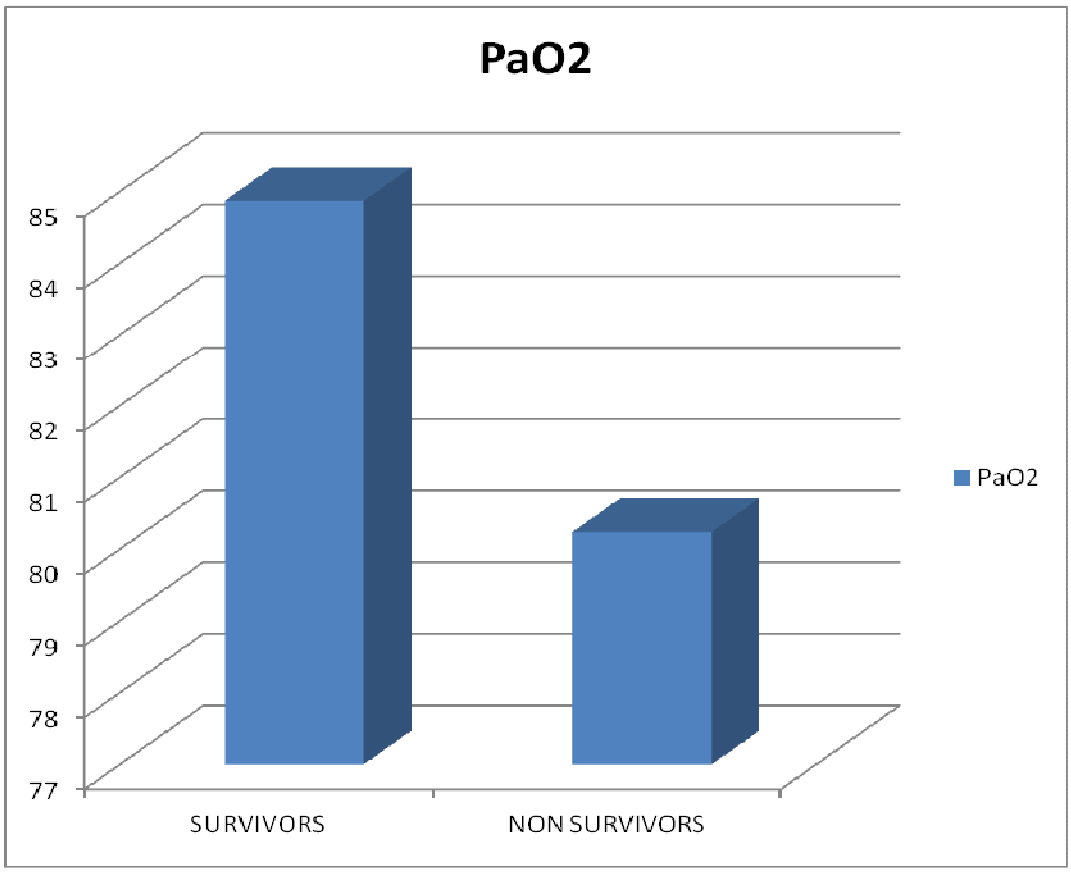


PaO2 AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
PaO2	84.87	6.372	80.24	13.897	0.094

PaO2 refers to the partial pressure of arterial oxygen. When its value were compared between the survivor group and the non survivor group, it was found that there was no significant relationship between PaO2 and mortality

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN PaO2 AND 30 DAYS MORTALITY

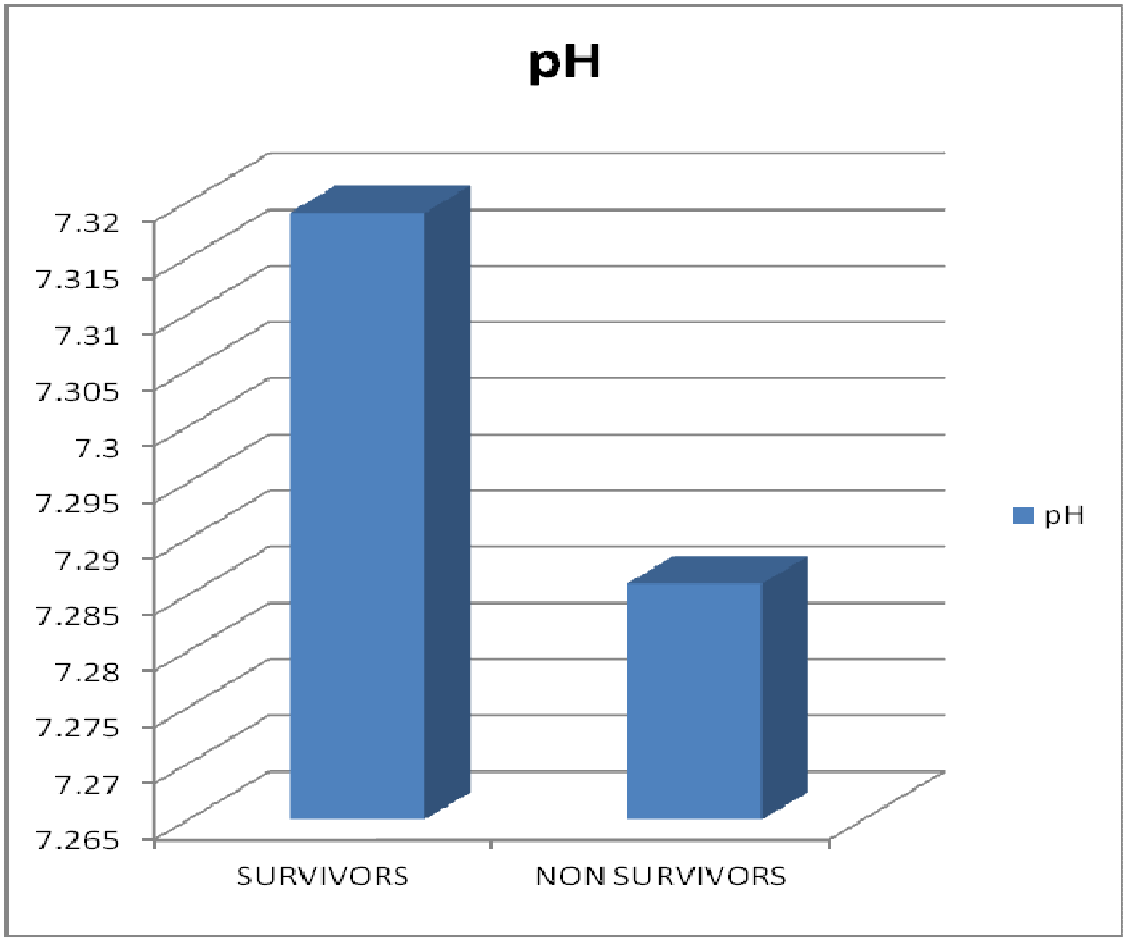


pH AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
pH	7.319	.0655	7.286	.0711	.026

The mean pH of survivors was 7.319 while that of non survivors was 7.286 and since the pH value is 0.026 which is less than 0.005, pH has independent correlation with mortality in type 2 diabetes patients with sepsis

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN pH AND 30 DAYS MORTALITY

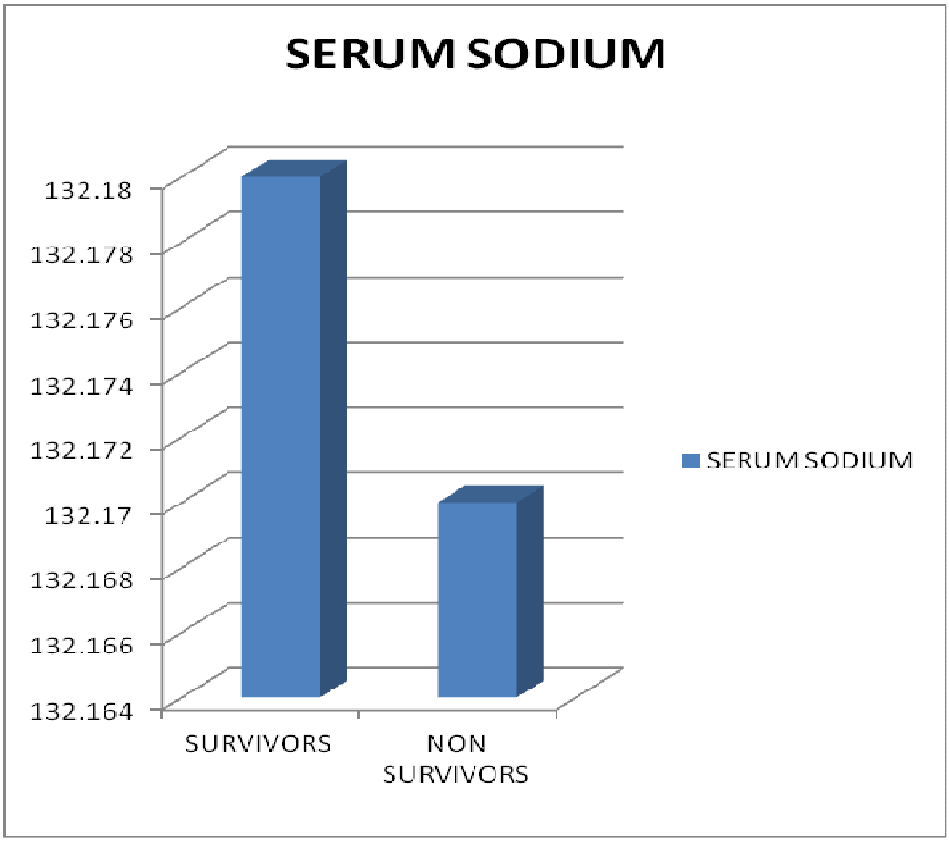


SERUM SODIUM AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
SERUM SODIUM	132.18	3.123	132.17	4.552	0.989

Serum sodium has an average value of 132 in both survivors and non survivors since the p value is more than 0.005, it indicates no significant correlation with mortality

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN SERUM SODIUM AND 30 DAYS MORTALITY

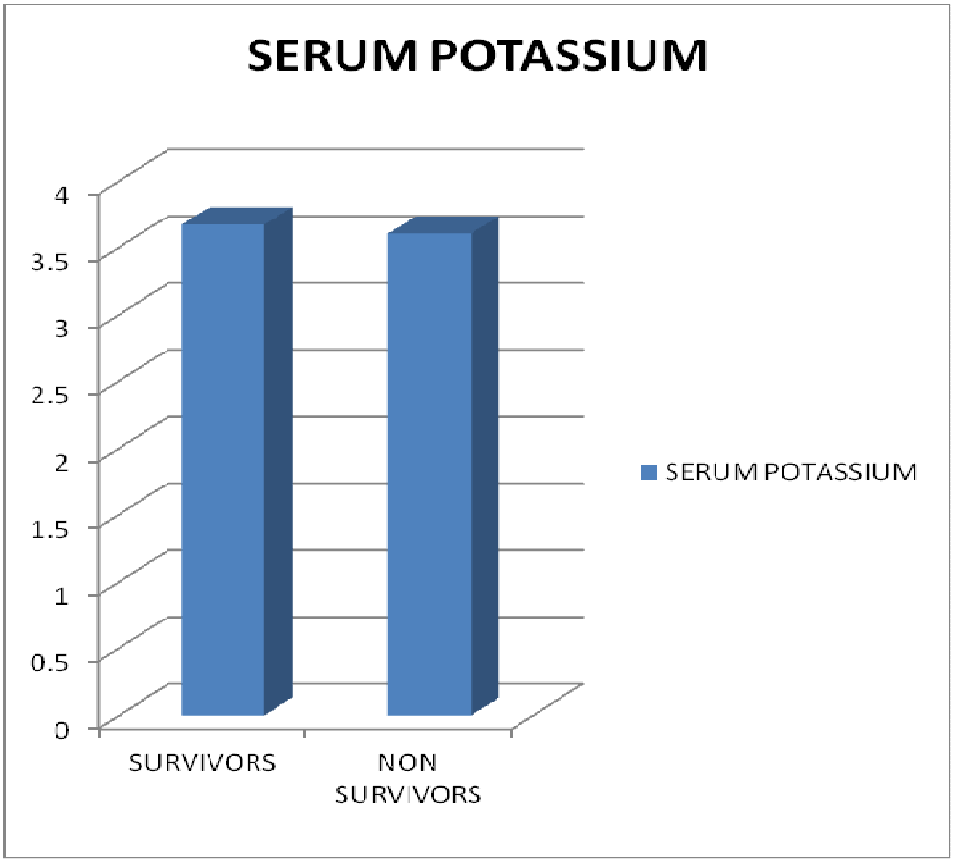


SERUM POTASSIUM AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
SERUM POTASSIUM	3.672	0.5655	3.603	1.0946	0.682

The average serum potassium value was 3.6 in both survivors and non survivors, so it implies than there is no correlation with mortality

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN SERUM POTASSIUM AND 30 DAYS MORTALITY

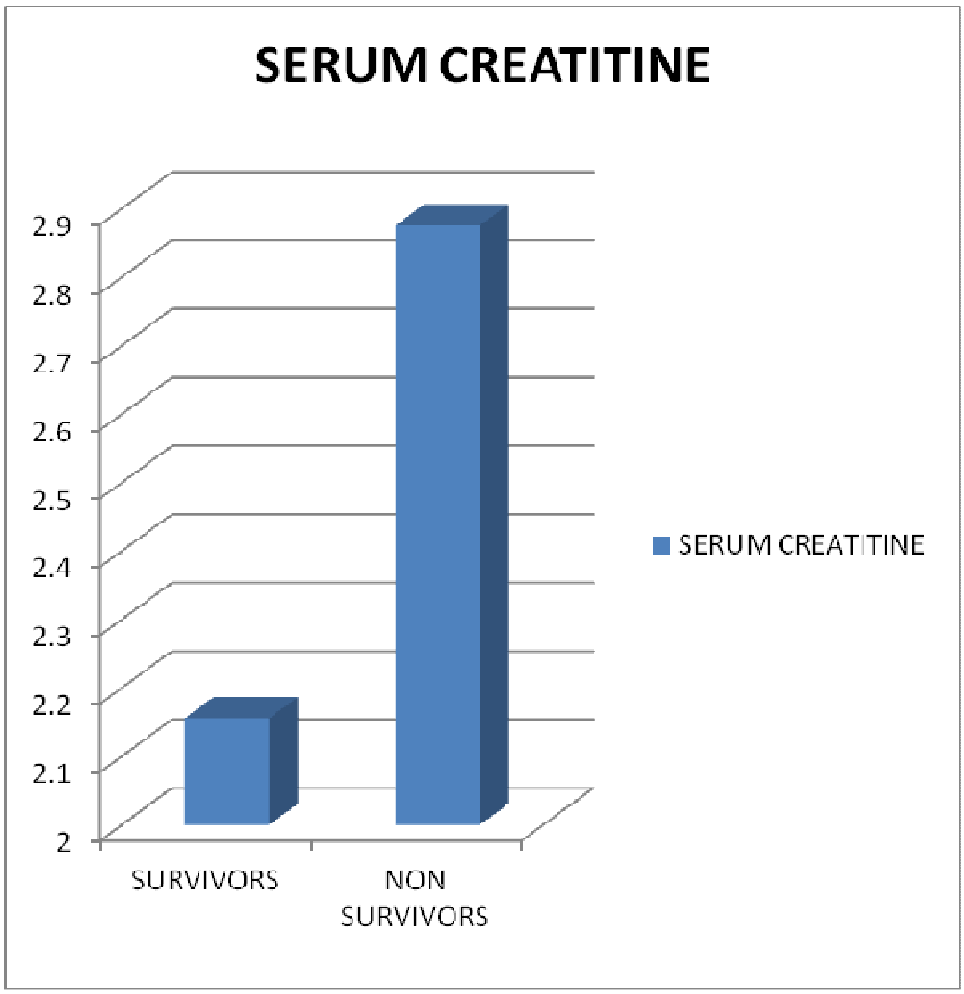


SERUM CREATININE AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
SERUM CREATININE	2.156	1.9385	2.876	.9542	0.015

Since the P value is less than 0.05 there is definite correlation between increased serum creatinine and mortality risk

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN SERUM CREATININE AND 30 DAYS MORTALITY

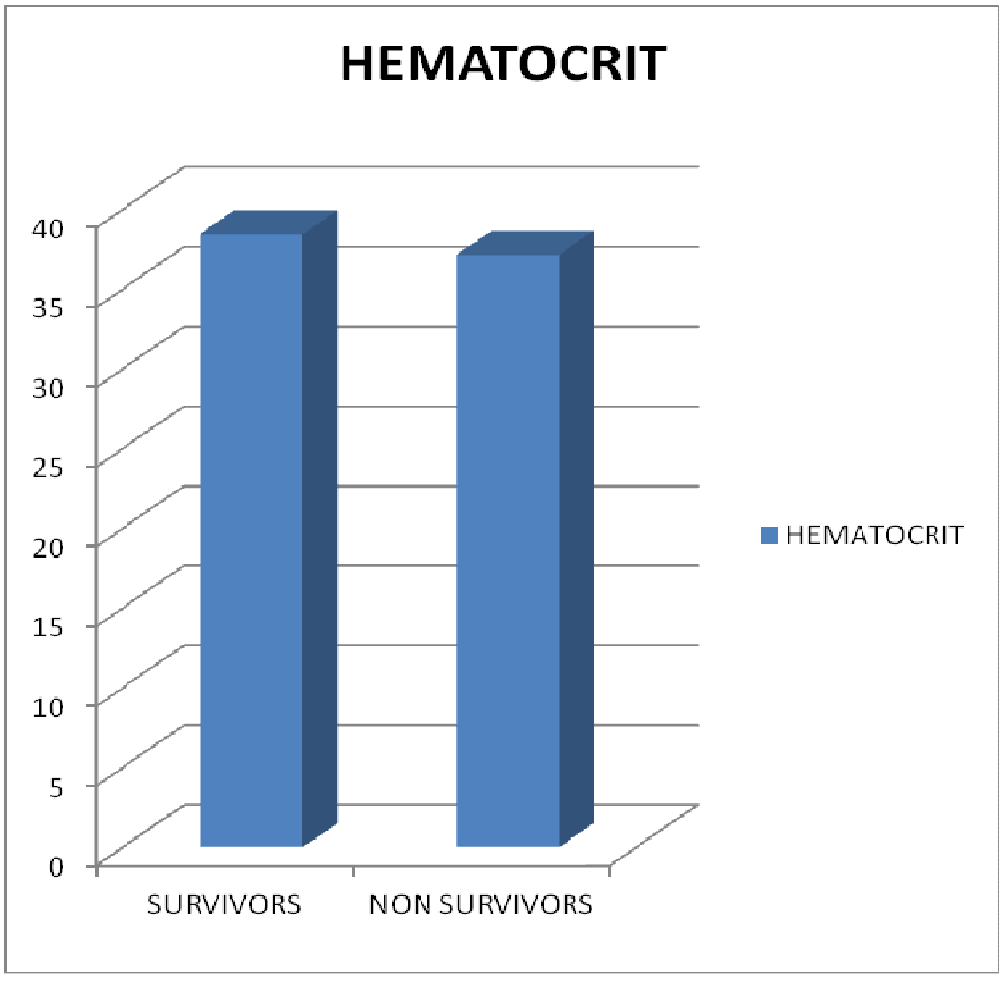


HEMATOCRIT AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
HEMATOCRIT	38.44	3.876	37.17	5.203	0.185

Hematocrit does not exhibit any definitive correlation with mortality in our study (P = 0.185)

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN HEMATOCRIT AND 30 DAYS MORTALITY



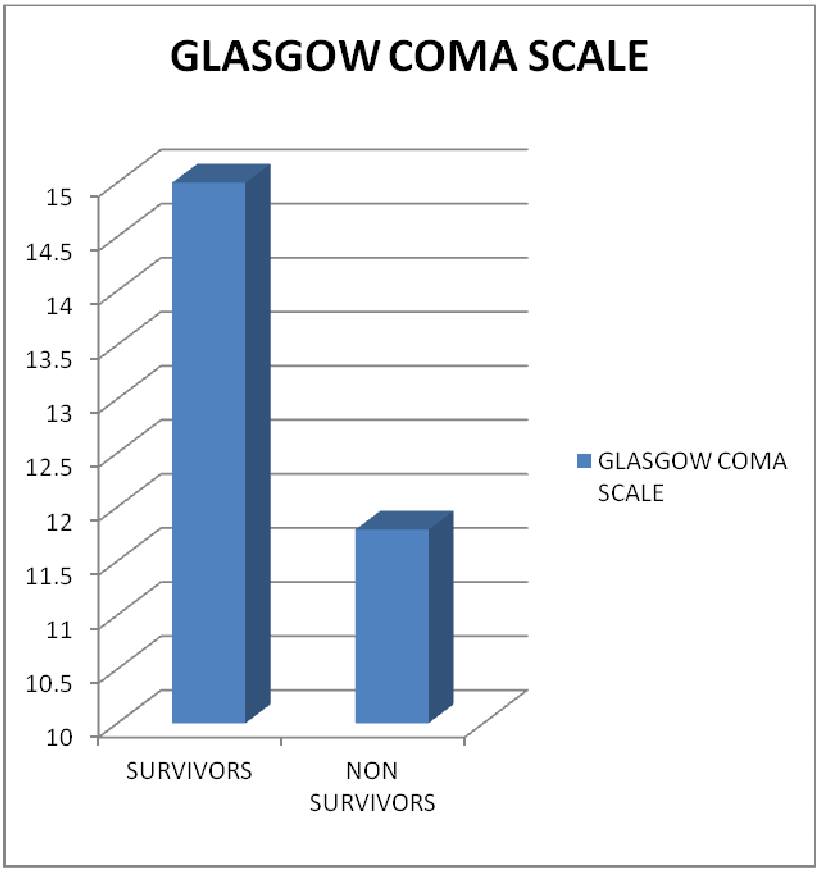
GLASGOW COMA SCALE AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
GLASCOW COMA SCALE	15.00	.000	11.79	1.934	<0.001**

Glasgow coma scale has an independent correlation with mortality in our study. A lower GCS appears to be associated with the higher mortality risk.

The mean GCS in survivors was 15 but in non survivors was 11

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN GLASCOW COMA SCALE AND 30 DAYS MORTALITY

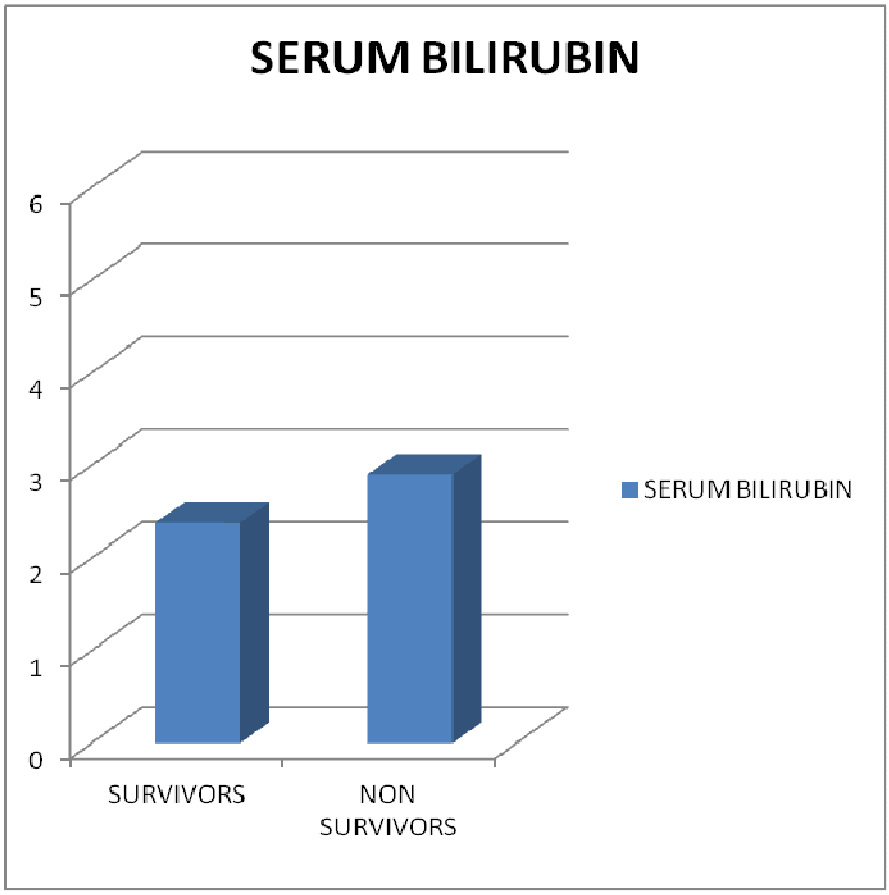


SERUM BILIRUBIN AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
SERUM BILIRUBIN	2.382	1.2864	2.903	1.1397	0.061

Serium bilirubin, which is one of the variable taken into account in the calculation of the sofa score has no significant correlation with mortality in our study

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN SERUM BILIRUBIN AND 30 DAYS MORTALITY

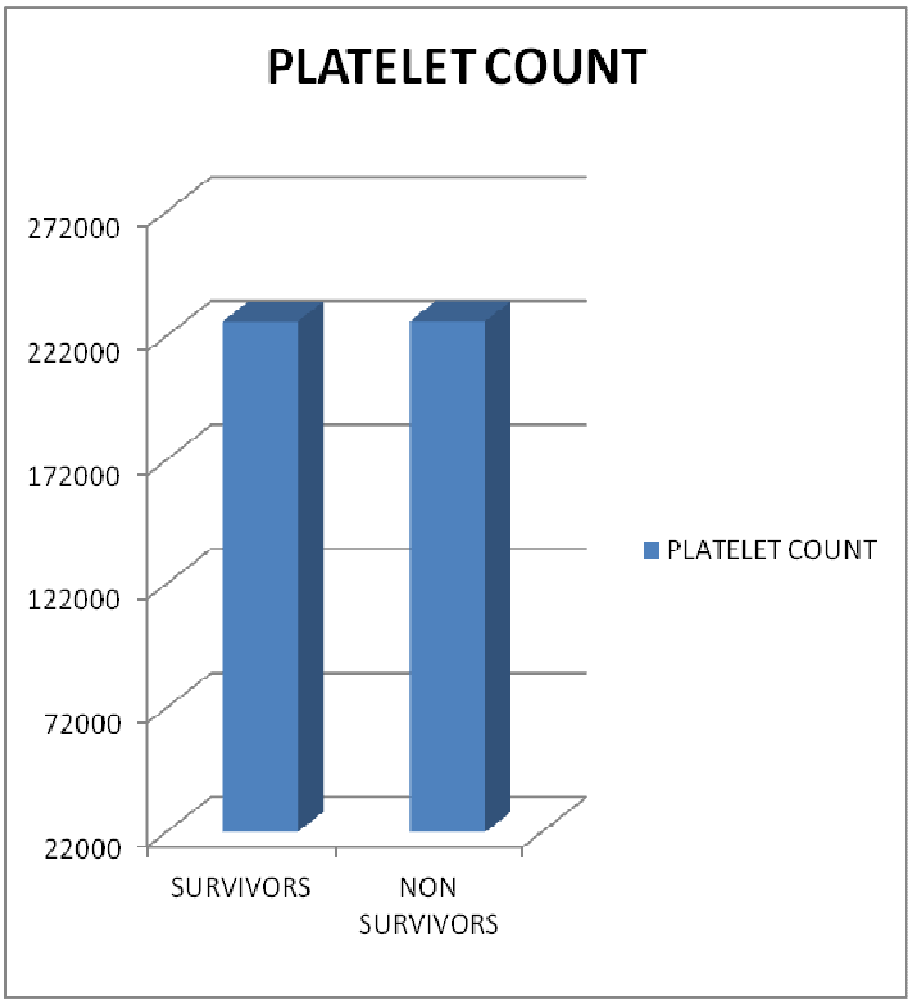


PLATELET COUNT AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
PLATELET COUNT	227881	110028	228089	178153	0.994

Platelet count does not exhibit any definitive correlation with mortality in our study (P = 0.994)

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN PLATELET AND 30 DAYS MORTALITY

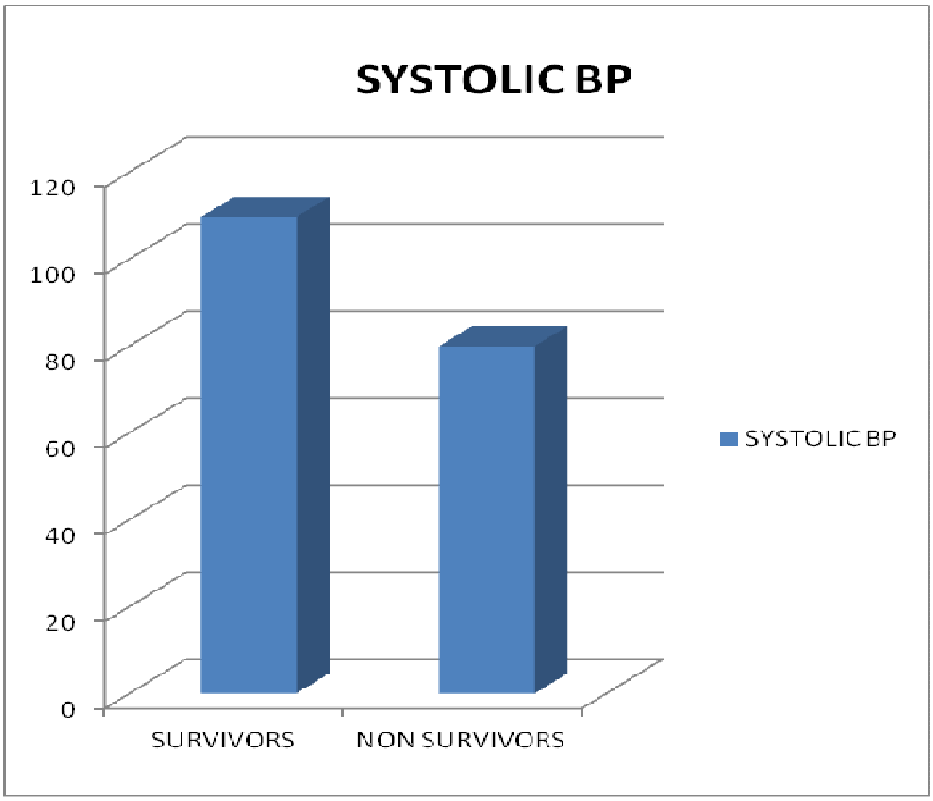


SYSTOLIC BP AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
SYSTOLIC BP	109.72	23.113	80.00	23.604	<0.001**

The average systolic blood pressure in survivors was 110 while that in non survivors was 80 mmHg. Since the p value was <0.001 (highly significant), systolic blood pressure has direct independent correlation with mortality.

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN SYSTOLIC BP AND 30 DAYS MORTALITY

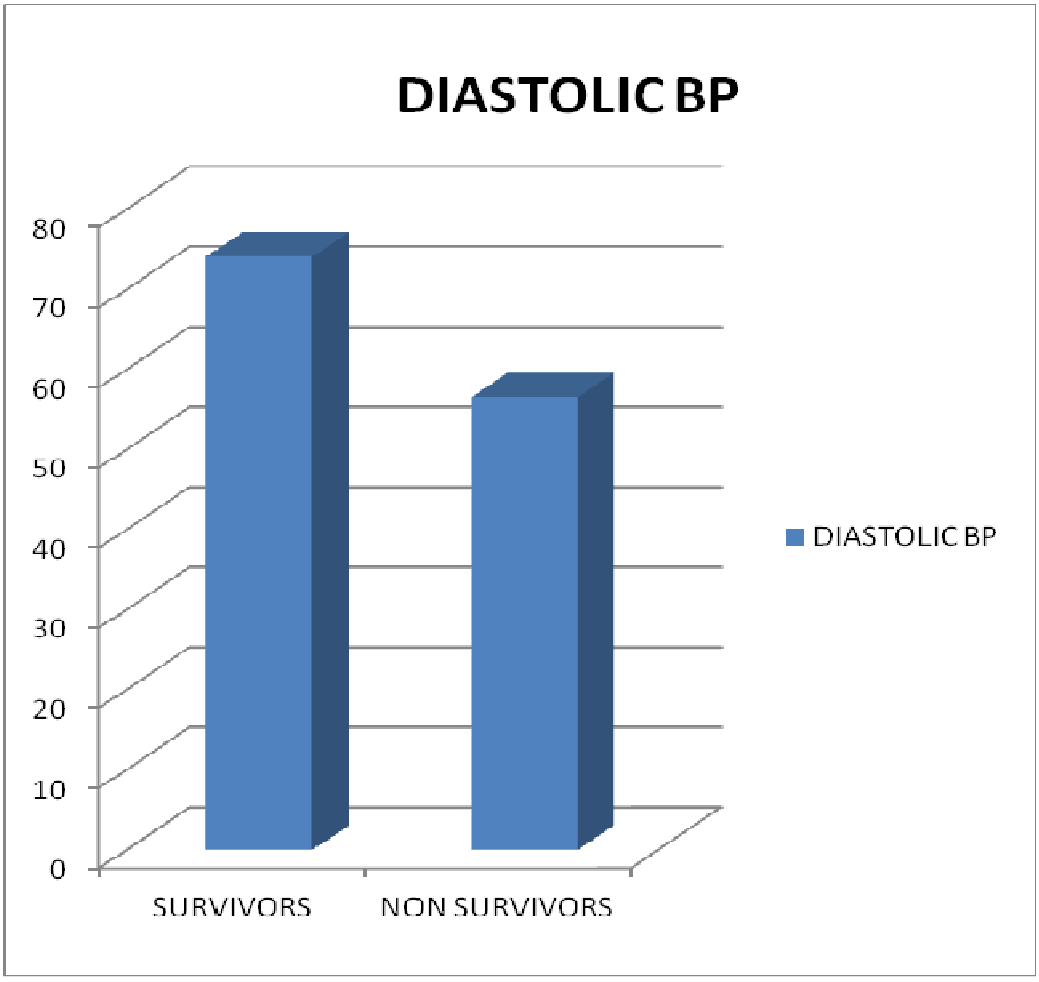


DIASTOLIC BP AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
DIASTOLIC BP	74.08	14.888	56.55	15.874	<0.001**

The average diastolic blood pressure in survivors was 74 while that in non survivors was 56 mmHg. Since the p value was <0.001 (highly significant), diastolic blood pressure has direct independent correlation with mortality.

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN DIASTOLIC BP AND 30 DAYS MORTALITY



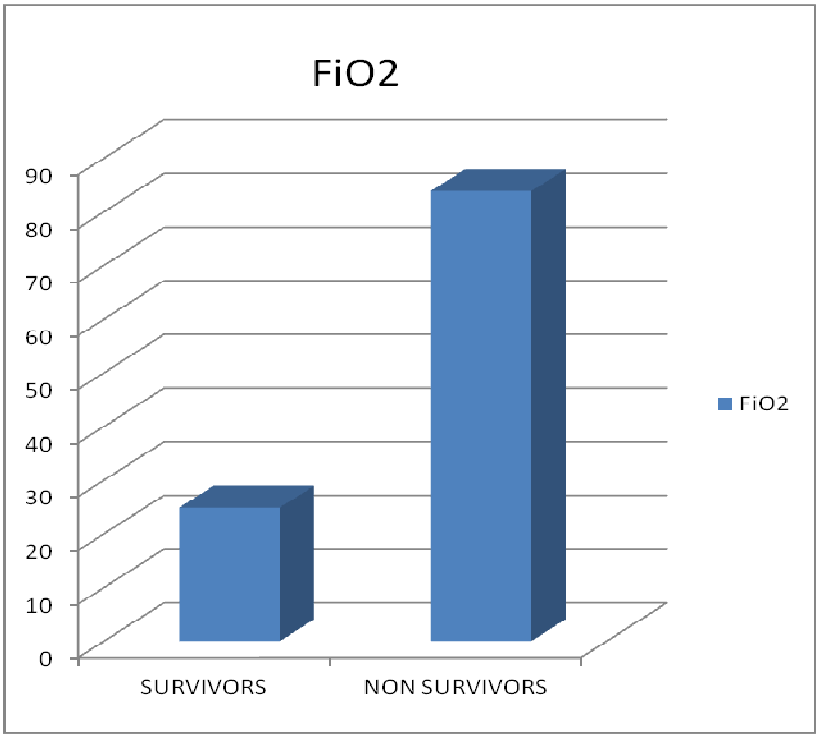
FiO2 AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
FiO2	24.89	11.644	83.86	18.448	<0.001**

FiO2 is fraction of inspired oxygen concentration which is one of the variables used in the calculation of SOFA SCORE and APACHE SCORE II.

The average FiO2 is survivors was found to be 24% while that in non survivors was 83% and since P value was <0.001 which is highly significant, FiO2 is found to have a positive correlation to mortality in our study

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN FiO2 AND 30 DAYS MORTALITY



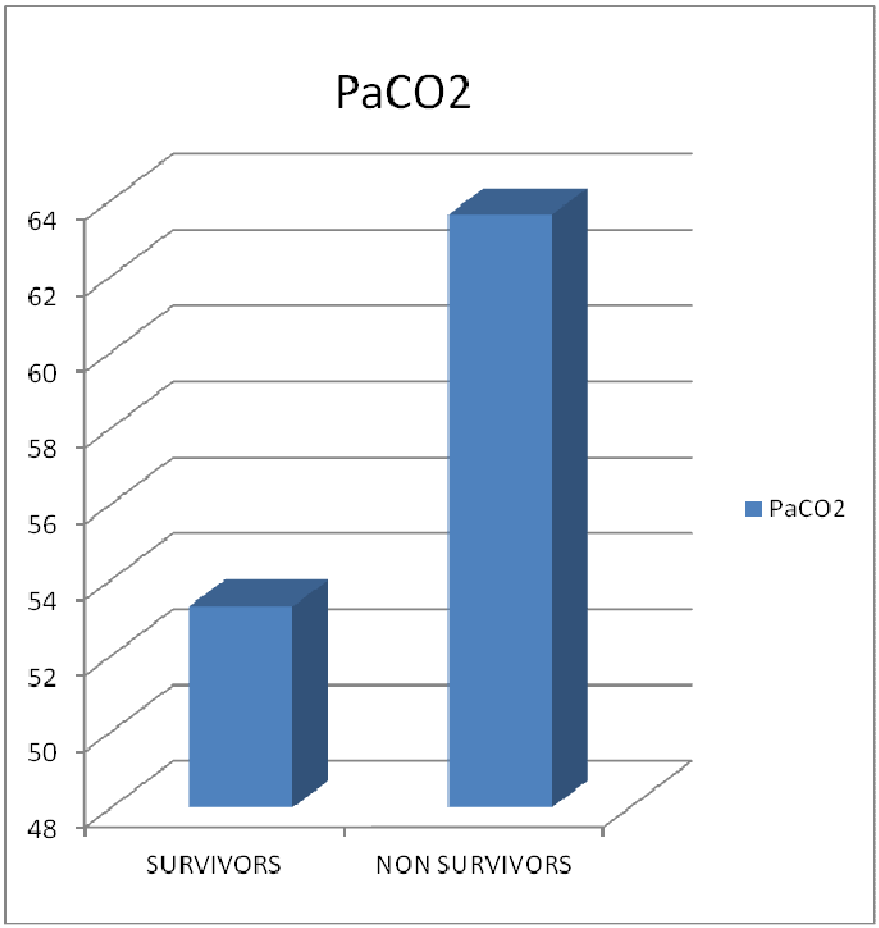
PaCO2 AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
PaCO2	53.30	11.105	63.62	10.645	<0.001**

Since the P value is less than 0.001, PaCO2 is an independent predicator of mortality in our study

The average PaCo2 in non survivors was found to be 63 while in survivors found to be 53

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN PaCO2 AND 30 DAYS MORTALITY

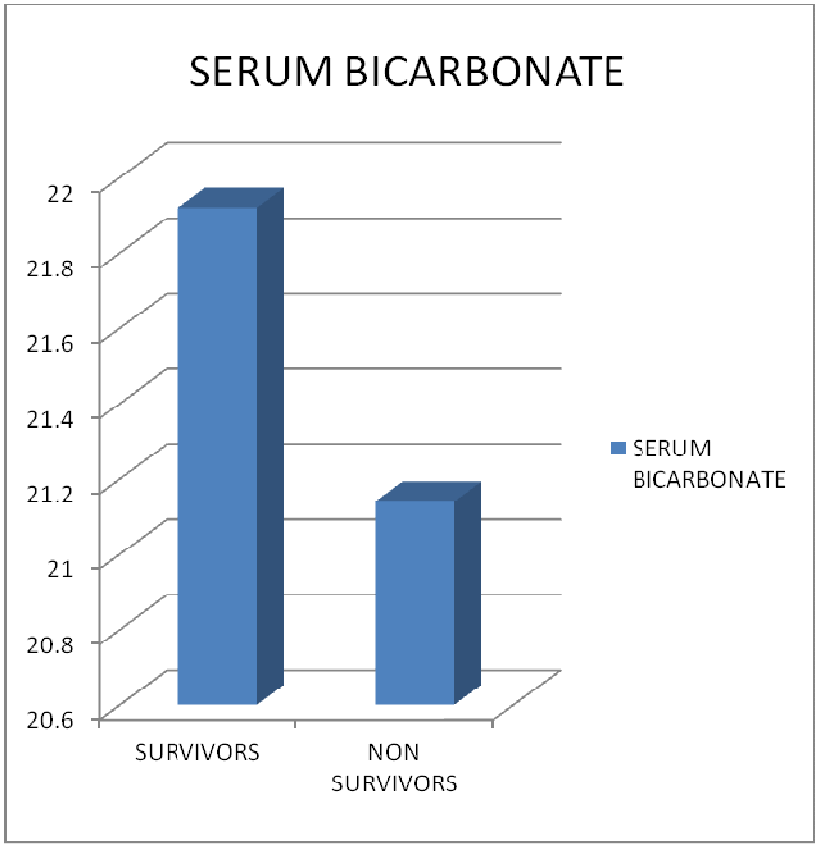


SERUM BICARBONATE AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
SERUM BICARBONATE	21.92	2.703	21.14	2.216	0.173

Serum Bicarbonate does not exhibit any definitive correlation with the mortality in our study (P = 0.173)

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN SERUM BICARBONATE AND 30 DAYS MORTALITY



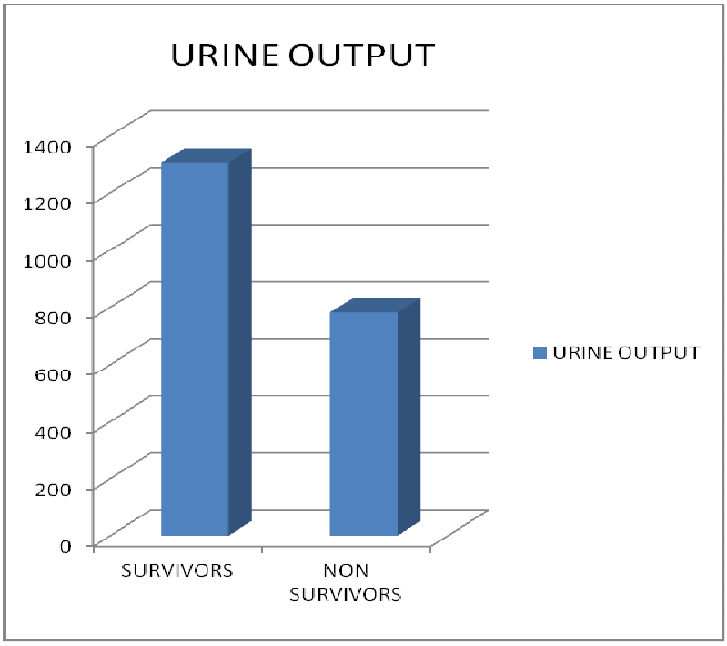
URINE OUTPUT AND ITS CORRELATION WITH 30 DAYS MORTALITY

PARAMETER	SURVIVORS		NON SURVIVORS		P VALUE
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	
URINE OUTPUT	1305.63	459.157	781.03	230.067	<0.001**

Urine output, which is one of the variables used in the calculation of SOFA score has an independent correlation with mortality in type 2 diabetes patients admitted with sepsis.

The urine output in non survivors was much lower than in survivors (average value 780 ml vs 1300 ml)

BAR DIAGRAM SHOWING THE CORRELATION BETWEEN URINE OUTPUT AND 30 DAYS MORTALITY



DISCUSSION

DISCUSSION

This study was conducted as a prospective observational study in type 2 diabetes patients admitted with sepsis in the medical wards of Madras Medical College, Rajiv Gandhi Government General hospital. The sample size was 100.After getting the informed consent of the patients and their attending close relatives, all the patients were subjected to history taking, physical examination, relevant laboratory testing and imaging. These tests were done to ascertain the presence of sepsis in selected patients.

Sepsis is a major cause of mortality in diabetic patients in our country. Hence better understanding of the disease course and etiopathogenesis is necessary. Prognostic scores like APACHE II and SOFA helps the physicians to triage the patients for early diagnosis and treatment of sepsis and its related complications which helps in reducing the mortality. It also helps the relatives of the patients in making improved decisions.

From our study it’s very clear that HbA1c is an independent prognostic factor for hospital mortality and length of hospitalisation for diabetes patients with sepsis. Admission plasma glucose has no correlation with mortality in our study.

Scoring systems such as APACHE II and SOFA are commonly used while evaluating the severity of illness and assessing prognosis of patients with sepsis.[1] They do not differentiate patients with poorly controlled diabetes as an important risk factor[1]. Diabetes is not included in chronic illness of APACHE II score.

Both APACHE II and SOFA score has shown good correlation with mortality and length of hospitalisation in patients with type 2 diabetes and sepsis.

Apart from these scores, some of their component variables namely temperature, heart rate, respiratory rate, blood pressure, Fio2, paco2, pao2, serum creatinine, pH, leukocyte count, GCS & urine output were also found to have significant correlation with mortality in diabetes patients with sepsis.

However serum sodium, potassium, bicarbonate, hematocrit, platelet count & bilirubin did not show any correlation with mortality in our study.

C Reactive protein (CRP), an acute phasic reactant was also found to have independent correlation with mortality.

The most important use of HbA1c as a prognostic factor is identification of diabetes patients with increased mortality risk among those with similar severity scores of sepsis (APACHE II and SOFA)[1]

Many articles published previously have shown increased risk for diabetes patients with sepsis but they do not consider glycoregulation prior to infection. According to the two major studies United Kingdom Prospective Diabetes Study (UKPDS) and Diabetes Control and Compications Trial (DCCT) long term glycoregulation assessed by HbA1c plays a major role in reducing chronic diabetes complications.

So proper regulation of blood sugar helps in reduction of mortality and also length of hospitalisation, if sepsis occurs. It plays a major role in reduction of overall mortality of patients with diabetes since sepsis is one of the leading causative factors of death.[1]

If patients with diabetes and sepsis are found to have higher HbA1c (>9), there is no difference in treatment option. Instead it helps in recognizing those patients with increased risk which leads to earlier detection and dealing with complications.

LIMITATIONS OF THE STUDY:

A multicentric study with large sample size and longer follow up is needed to assess whether HbA1c can be used as prognostic factor in type 2 diabetes patients with sepsis.

CONCLUSION

CONCLUSION

HbA1c, APACHE II score, SOFA score, CRP ,total leukocyte count were found to have significant correlation with 30 DAYS mortality and length of hospitalisation.

Admission plasma glucose has no correlation with mortality and length of stay in our study.

HbA1c has correlation with CRP, APACHE II score, SOFA score but not with admission plasma glucose levels.

HbA1c is as efficacious as both APACHE II score and SOFA score as a prognostic factor in diabetes patients with sepsis

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BIBLIOGRAPHY

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ANNEXURES

PROFORMA

Name: Age/Sex :

IP No : Address :

Patient ID No : Occupation :

SYMPTOMS:

Fever:

Cough/ burning micturition/ loose stools/ vomiting/ abdominal pain/seizures/ skin / soft tissue infections:

PAST HISTORY:

Chronic renal disease

Chronic liver disease

Malignancy

Immunosuppressive drugs

Pregnancy: yes/no

GENERAL EXAMINATION:

GCS:

Pallor/icterus/cyanosis/clubbing/pedal edema/gen lymphadenopathy

VITALS:

BP:

PR:

RR:

Temp:

SYSTEMIC EXAMINATION:

CVS:

RS:

ABDOMEN:

CNS:

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.K.Lavanya
Post Graduate in M.D. General Medicine
Madras Medical College
Chennai 600 003

Dear Dr. K.Lavanya,

The Institutional Ethics Committee has considered your request and approved your study titled **"STUDY ON THE ROLE OF HBAIC AS A PROGNOSTIC FACTOR IN TYPE 2 DIABETES PATIENTS WITH SEPSIS " - NO.09032016.**

The following members of Ethics Committee were present in the meeting hold on **01.03.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.R.Vimala,MD.,Dean,MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD.,Inst.of Pharmacology,MMC,Ch-3	: Member
5.Prof.P.Raghumani,MS, Dept.of Surgery,RGGGH,Ch-3	: Member
6.Dr.Baby Vasumathi, Director, Inst. of O&G,Ch-8	: Member
7.Prof.M.Saraswathi,MD.,Director, Inst.of Path,MMC,Ch-3	: Member
8.Prof.Srinivasagalu,Director,Inst.of Int.Med.,MMC,Ch-3	: Member
9.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
10.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
11.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

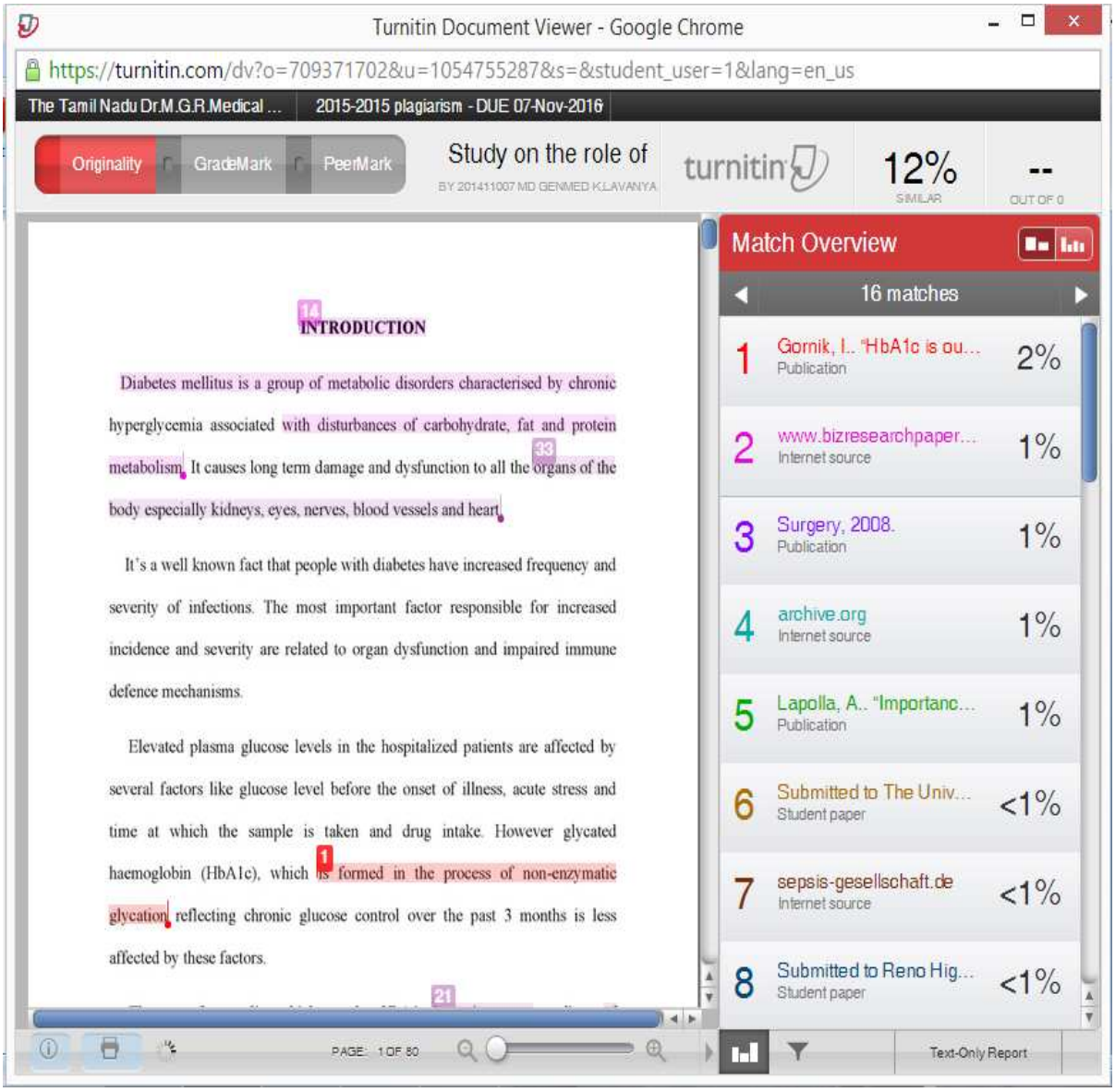
We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

TURNITIN PLAGIARISM SCREENSHOT



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INTRODUCTION

INFORMATION SHEET

We are conducting a study on **"STUDY ON THE ROLE OF HBA1C AS A PROGNOSTIC FACTOR IN TYPE 2 DIABETES PATIENTS WITH SEPSIS"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to decide whether HbA1c can be used as a prognostic factor in type 2 diabetes patients with sepsis for better management.

We are selecting certain cases and if you are found eligible, we may be using your specimen to perform extra tests and special studies which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator	Signature of Participant

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜீவ் காந்தி அரசு பொது மருத்துவமனையில் ஒரு ஆராய்ச்சி நடைபெற்று வருகிறது. இதில் சீழ்ப்பிடிப்பு கொண்ட இரண்டாம் வகை நீரிழிவு நோயாளிகளுக்கு ஒரு முன்கணிப்பு காரணி என HbA1c பங்கு பற்றிய ஆராய்ச்சி செய்கிறோம்.

அதற்கு சர்க்கரையின் கட்டுப்பாட்டு அளவை அறிய இரத்தப் பரிசோதனை அவசியம். அதற்கு தங்கள் ஒத்துழைப்பு தேவை.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்புப் பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவில் தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி:

PATIENT CONSENT FORM

Study Detail	:	STUDY ON THE ROLE OF HBA1C AS A PROGNOSTIC FACTOR IN TYPE 2 DIABETES PATIENTS WITH SEPSIS
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
Identification no.	:	

Patient may check (☑) these boxes

1. I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑
2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑
3. I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑
4. I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from ❑

any deterioration in my health or well being or any unexpected or unusual symptoms.

5. I hereby consent to participate in this study. ❑
6. I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ❑

Signature/thumb impression	Signature of Investigator
Patient's Name and Address:	Study Investigator's Name: **Dr. K. LAVANYA**

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு:-

சீழ்ப்பிடிப்பு கொண்ட இரண்டாம் வகை நீரிழிவு நோயாளிகளுக்கு ஒரு முன்கணிப்பு காரணி என HbA1c பங்கு பற்றிய ஆய்வு:-

பெயர் : தேதி:

வயது : உள்நோயாளி எண்:

பால் : ஆராய்ச்சி சேர்க்கை எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது. எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன்.

சீழ்ப்பிடிப்பு கொண்ட இரண்டாம் வகை நீரிழிவு நோயாளிகளுக்கு HbA1c பரிசோதனைப்பற்றி ஆராய்ச்சியாளர் கூற முழுவதும் விளங்கப் பெற்றேன்.

மேற்கொண்ட பரிசோதனையின் போது ஏற்படக்கூடிய பின் விளைவுகளையும் முழுவதும் உணர்ந்து இந்த பரிசோதனைக்கு மனமாற சம்மதிக்கிறேன்.

கையொப்பம்

MASTER CHART

S.No	Patient age	Sex	Admission CBG	HbA1C	CRP	Apache	Sofa	Duration	temp (F)	heart rate	BP - systolic	BP - Diastolic	respiratory rate	FiO2	PaCo2	PaO2	Na+	K+	Creatinine	Ph	HCo3	WBC	PCV	GCS	CHP	Platelet count	Billirubin	Urine O/p	Respiratory Support
1	54	M	300	8.1	76	11	3	4	99.1	110	100	70	30	21	55	76	130	4	1.3	7.3	22	13662	40	15	0	259298	1.5	1500	No
2	45	F	276	7.6	102	12	4	6	99.9	120	90	60	25	21	44	79	135	3.3	1.3	7.32	22	14395	38	15	0	154998	2	1500	No
3	64	M	302	8.8	250	25	9	Death	99.4	140	80	60	21	80	65	76	135	3	2	7.2	20	20872	40	15	0	154560	2.4	800	Yes
4	75	F	190	9.5	401	30	14	Death	99.8	135	70	50	25	95	86	56	130	2.5	2.2	7.2	20	20605	30	15	0	509743	4	500	Yes
5	35	F	225	7	66	7	3	5	98.2	96	100	70	30	21	56	88	136	2.7	1.4	7.4	22	13850	33	15	0	252458	2	2000	No
6	50	M	196	7.5	56	13	5	6	96.1	96	130	70	22	21	76	76	128	3	2	7.4	26	14445	45	15	0	204282	2	1500	No
7	58	M	401	8.1	202	19	6	14	100.3	135	150	100	26	21	62	88	130	3	2.5	7.22	18	8487	38	15	0	88869	5	500	No
8	68	F	370	9.8	560	31	11	Death	102.6	150	70	50	28	80	56	106	128	2.8	3	7.3	20	24704	40	13	0	187216	4.5	700	Yes
9	40	F	201	7.1	35	10	3	3	98.2	110	100	70	22	21	28	85	135	4	1.8	7.3	20	14814	35	15	0	304606	2	1500	No
10	65	M	256	10.7	486	27	13	Death	101.8	135	70	50	30	90	29	96	134	3	2.5	7.35	22	20920	42	9	0	605274	4.4	600	Yes
11	45	M	180	7.3	65	10	4	5	98.1	110	100	70	20	21	27	92	136	4.2	0.8	7.3	18	11527	36	15	0	92606	3.2	1500	No
12	56	F	210	7.6	103	14	4	7	98.8	125	90	60	26	21	56	88	134	3	2	7.4	20	14287	40	15	0	452268	3.5	1500	No
13	65	M	301	8.8	300	26	8	Death	99.2	130	160	110	26	21	56	82	128	2.8	2.8	7.3	20	14300	32	12	0	104575	3	800	No
14	35	F	192	7	46	10	4	4	98.9	76	90	60	22	21	56	96	128	4	1.5	7.3	22	7433	33	15	0	121609	2.8	1500	No
15	52	M	226	7.4	81	12	3	5	101.9	110	130	90	24	21	52	78	128	4.2	1.6	7.36	20	16878	32	15	0	401866	1.4	1500	No
16	50	M	425	9.2	276	28	10	Death	102.6	40	80	60	30	80	62	90	130	5	3	7.2	23	7383	40	12	0	158706	1.6	1000	Yes
17	38	F	160	7.2	78	10	4	6	97.5	120	90	60	26	21	46	76	138	4	2	7.4	26	16681	38	15	0	242579	1.8	1000	No
18	49	F	180	11.5	576	33	15	Death	101.9	140	70	50	32	90	58	65	126	2.5	2.3	7.31	18	32616	32	11	0	77628	4.6	600	Yes
19	42	M	186	6.9	36	8	3	2	97.3	110	120	70	24	21	48	76	130	4	0.8	7.3	25	8927	38	15	0	505014	2.4	1200	No
20	61	M	310	8.3	220	21	6	15	100.8	140	150	100	27	21	67	91	132	3	2.5	7.22	19	11361	39	15	0	203463	5.1	500	No
21	51	M	201	7.2	76	13	4	4	99.6	110	90	60	22	21	45	82	135	4.5	2.2	7.3	20	16514	38	15	0	301794	1.4	1500	No
22	33	F	156	7.3	54	11	3	3	98.8	125	90	60	24	16	64	78	130	4	1.8	7.2	18	16777	30	15	0	257533	2.11	1500	No
23	68	F	200	12.7	476	29	12	Death	104.1	155	90	60	33	90	66	79	132	5	4	7.4	22	13778	29	11	0	209097	1.7	800	Yes
24	44	M	207	7	38	10	3	4	98.4	110	100	70	26	21	48	82	128	3	1.4	7.4	26	14645	36	15	0	189652	1.2	1800	No
25	61	M	539	7.8	96	16	4	6	100.8	120	90	60	22	21	60	78	129	4.1	2.6	7.3	20	14440	42	15	0	152242	1.6	1500	No
26	52	F	186	9.8	290	32	15	Death	104.8	136	70	50	28	80	62	79	135	4	3	7.3	22	25673	28	11	0	79393	2.4	1500	Yes
27	34	M	170	6.9	35	11	4	5	97.9	110	140	90	24	21	46	78	134	4.6	2.6	7.3	22	14521	36	15	0	255563	1.3	1500	No
28	41	F	210	7.5	71	13	5	6	99.3	120	90	60	23	21	52	85	130	4	2	7.3	22	17977	29	15	0	121392	2	1700	No
29	49	M	236	7.8	42	14	6	7	101.1	130	80	60	22	35	56	88	130	4	1.8	7.3	22	16797	43	15	0	203015	1.4	1500	No
30	73	F	235	10.3	234	32	17	Death	104.7	145	70	50	28	85	66	78	130	2.8	6	7.3	14	14931	38	12	0	77623	2.6	500	Yes
31	34	M	202	7.2	63	10	3	3	98.2	80	100	70	16	85	56	85	130	4	3	7.35	22	12376	43	15	0	204224	1.5	2000	No
32	59	F	311	8.2	226	22	6	15	100.3	144	150	100	28	21	66	91	131	3	2.5	7.22	20	9716	41	15	0	90370	5	500	No
33	45	F	250	7.8	201	12	5	7	99.5	115	90	70	25	25	40	96	135	3	1.5	7.36	20	12466	40	15	0	107352	2.1	1500	No
34	76	M	176	11.5	583	32	15	Death	102.4	130	60	40	33	100	61	71	130	3	2	7.2	20	14898	39	12	0	99666	2.0	800	Yes
35	42	M	152	8.1	56	4	3	2	98.3	90	110	90	19	35	42	84	130	3	1.3	7.4	18	14974	40	15	0	154164	1.0	200	No
36	38	F	176	7.5	31	10	5	4	97.6	110	130	80	22	35	41	76	130	4	1.5	7.31	20	15859	36	15	0	163063	2.3	1000	No
37	61	M	310	8.3	220	21	6	15	100.8	140	150	100	27	21	67	91	132	3	2.5	7.22	19	11361	39	15	0	203463	5.1	500	No
38	31	F	601	7.6	36	4	3	3	98.3	95	90	60	16	35	45	91	132	3.6	1.4	7.36	21	14500	38	15	0	209729	1.0	1700	No
39	58	F	180	9.8	180	30	14	Death	103.6	130	70	50	32	95	58	75	135	5	2	7.3	20	17932	41	12	0	145545	2.0	1200	Yes
40	55	M	301	8.1	94	10	3	5	100.7	120	100	70	20	40	55	86	130	3	1	7.5	26	13788	40	15	0	253931	1.5	1000	No
41	47	F	356	11	506	30	14	Death	99.3	135	70	50	25	95	86	55	130	2.5	2.2	7.2	20	20508	33	15	0	508203	4.1	500	Yes
42	45	F	256	7.1	36	12	4	5	99.6	110	100	70	30	21	55	76	130	4	13	7.3	22	13824	40	15	0	111014	2.0	1500	No
43	55	F	280	7.5	90	12	3	7	101.7	110	130	90	24	21	46	78	128	4.2	1.6	7.36	20	16362	32	15	0	401648	1.5	1600	No
44	69	M	539	7.8	96	16	4	6	100.8	120	90	60	22	21	60	78	129	4.1	2.6	7.3	20	14440	42	15	0	152242	1.6	1500	No
45	52	M	300	7.8	86	12	3	6	101.7	110	130	90	24	21	47	78	128	4.2	1.6	7.3	20	16323	33	15	0	401322	1.4	1400	No
46	51	M	230	7	26	13	4	4	99.6	110	90	60	22	21	22	82	135	4.5	2.2	7.3	20	16519	38	15	0	309523	1.6	1500	No
47	58	M	302	8.2	201	19	6	14	100.8	135	150	100	26	21	62	88	130	3	2.5	7.22	18	8825	37	15	0	201389	5.1	500	No
48	68	F	288	12.6	376	29	12	Death	104.2	156	90	60	33	90	66	79	132	5.1	4	7.4	22	13741	29	11	0	204071	1.7	800	Yes
49	55	M	436	10.1	180	19	6	10	100.8	136	150	100	26	21	63	88	130	3.2	2.5	7.26	18	8851	37	15	0	209992	5.0	500	No
50	35	F	160	7.1	26	10	4	4	98.6	76	90	60	22	21	56	96	128	4	1.5	7.3	22	7517	33	15	0	121966	2.8	1500	No
51	56	M	312	8.2	102	13	3	5	99.1	118	100	70	32	21	57	78	131	4	1.3	7.3	24	15408	42	15	0	263205	1.5	1500	No
52	47	F	288	7.7	119	15	4	7	99.9	125	90	60	26	21	48	80	136	3.3	1.3	7.32	23	16879	40	15	0	156972	2	1500	No
53	66	M	308	8.9	266	28	9	Death	99.4	147	80	60	23	80	67	78	136	3	2	7.2	21	22954	43	15	0	157541	2.4	800	Yes
54	63	M	401	8.1	202	19	6	14	100.3	135	150	100	26	21	62	88	130	3	2.5	7.22	18	8487	38	15	0	88869	5	500	No
55	38	F	230	7.1	79	10	3	6	98.2	103	100	70	33	21	61	90	139	2.7	1.4	7.4	24	16682	35	15	0	256033	2	2000	No
56	52	M	654	7.6	72	15	5	7	96.1	105	130	70	25	21	80	79	131	3	2	7.4	29	17400	47	15	0	206070	2	1500	No
57	59	M	311	8.2	226	22	6	15	100.3	144	150	100	28	21	66	91	131	3	2.5	7.22	20	9716	41	15	0	90370	5	500	No
58	69	F	383	9.9	575	32	11	Death	102.6	157	70	50	31	80	59	108	129	2.8	3	7.3	21	26601	42	13	0	190186	4.5	700	Yes
59	42	F	215	7.2	49	12	3	4	98.2	119	100	70	23	21	49	87	138	4	1.8	7.3	23	16426	37	15	0	306734	2	1500	No
60	64	M	264	10.8	498	28	13	Death	101.8	143	70	50	33	90	60	99	135	3	2.5	7.35	23	23684	45	9	0	606621	4.4	600	Yes
61	48	M	190	7.4	82	11	4	6	98.1	117	100	70	22	21	43	95	137	4.2	0.8	7.3	20	14245	38	15	0	93928	3.2	1500	No
62	59	F	467	7.7	126	15	4	8	98.8	132	90	60	28	21	61	90	136	3	2	7.4	22	17187	42	15	0	454631	3.5	1500	No

S.No	Patient age	Sex	Admission CBG	HbA1C	CRP	Apache	Sofa	Duration	temp (F)	heart rate	BP - systolic	BP - Diastolic	respiratory rate	FiO2	PaCo2	PaO2	Na+	K+	Creatinine	Ph	HCo3	WBC	PCV	GCS	CHP	Platelet count	Billirubin	Urine O/p	Respiratory Support
63	67	M	315	8.9	315	28	8	Death	99.2	135	160	110	29	21	57	83	131	2.8	2.8	7.3	21	15547	35	12	0	106580	3	800	No
64	36	F	202	7.1	66	11	4	5	98.9	83	90	60	24	21	61	97	130	4	1.5	7.3	24	9452	35	15	0	125074	2.8	1500	No
65	54	M	232	7.5	100	14	3	6	101.9	117	130	90	26	21	55	80	129	4.2	1.6	7.36	22	18752	34	15	0	403890	1.4	1500	No
66	71	M	312	9.3	301	29	10	Death	102.6	50	80	60	33	80	64	91	132	5	3	7.2	26	9399	43	12	0	161555	1.6	1000	Yes
67	40	F	173	7.3	102	13	4	7	97.5	129	90	60	27	21	49	77	139	4	2	7.4	27	19377	41	15	0	245882	1.8	1000	No
68	77	F	192	11.6	606	36	15	Death	101.9	146	70	50	35	90	62	66	129	2.5	2.3	7.31	21	35279	34	11	0	81048	4.6	600	Yes
69	44	M	200	7	66	10	3	3	97.3	117	120	70	25	21	53	77	131	4	0.8	7.3	26	10737	41	15	0	508869	2.4	1200	No
70	83	F	248	10.3	322	36	15	Death	104.4	146	70	50	30	85	66	98	148	5.8	4	7.3	19	26757	40	9	0	129754	2	700	Yes
71	53	M	210	7.3	102	16	4	5	99.6	119	90	60	24	21	50	83	136	4.5	2.2	7.3	23	18299	40	15	0	305329	1.4	1500	No
72	35	F	168	7.4	72	14	3	4	98.8	135	90	60	25	16	68	81	133	4	1.8	7.2	21	18371	33	15	0	258901	2.11	1500	No
73	71	F	205	12.8	503	30	12	Death	104.1	160	90	60	36	90	67	81	135	5	4	7.4	24	15896	31	11	0	211697	1.7	800	Yes
74	45	M	212	7.1	52	12	3	5	98.4	115	100	70	27	21	53	84	130	3	1.4	7.4	27	17631	38	15	0	192634	1.2	1800	No
75	64	M	378	7.9	124	18	4	7	100.8	126	90	60	25	21	62	80	131	4.1	2.6	7.3	21	16427	45	15	0	154735	1.6	1500	No
76	58	M	401	8.1	202	19	6	14	100.3	135	150	100	26	21	62	88	130	3	2.5	7.22	18	8487	38	15	0	88869	5	500	No
77	37	M	176	7	47	12	4	6	97.9	118	140	90	25	21	29	79	137	4.6	2.6	7.3	24	15633	38	15	0	256944	1.3	1500	No
78	42	F	222	7.6	90	15	5	7	99.3	126	90	60	26	21	53	88	131	4	2	7.3	23	20726	32	15	0	122977	2	1700	No
79	51	M	244	7.9	62	15	6	8	101.1	138	80	60	24	35	61	89	131	4	1.8	7.3	24	19091	46	15	0	204649	1.4	1500	No
80	59	F	467	7.7	126	15	4	8	98.8	132	90	60	28	21	61	90	136	3	2	7.4	22	17187	42	15	0	454631	3.5	1500	No
81	35	M	215	7.3	81	13	3	4	98.2	89	100	70	18	85	59	86	131	4	3	7.35	25	14967	45	15	0	207691	1.5	2000	No
82	83	F	280	9.9	383	32	13	Death	101.4	129	70	50	31	90	61	67	129	3	2	7.31	24	17363	38	12	0	82784	2.2	750	Yes
83	46	F	265	7.9	225	14	5	8	99.5	122	90	70	26	25	45	98	138	3	1.5	7.36	23	14155	43	15	0	108865	2.1	1500	No
84	77	M	187	11.6	605	35	15	Death	102.4	138	60	40	34	100	63	74	131	3	2	7.2	22	17058	41	12	0	101972	2	800	Yes
85	43	M	157	8.2	81	5	3	3	98.3	97	110	90	22	35	47	85	133	3	1.3	7.4	21	16227	42	15	0	156607	1	200	No
86	39	F	183	7.6	47	13	5	5	97.6	117	130	80	25	35	44	77	133	4	1.5	7.31	21	17484	38	15	0	166950	2.3	1000	No
87	70	M	314	10.2	247	35	15	Death	102.9	140	80	60	25	85	63	80	123	4	4.1	7.2	19	23387	37	8	0	191849	2.6	900	Yes
88	32	F	533	7.7	46	6	3	4	98.3	102	90	60	18	35	48	93	135	3.6	1.4	7.36	23	15937	40	15	0	212017	1	1700	No
89	77	F	188	9.9	195	33	14	Death	103.6	140	70	50	34	95	63	78	138	5	2	7.3	22	20566	43	12	0	147050	2	1200	Yes
90	58	M	307	8.2	119	13	3	6	100.7	129	100	70	21	40	56	88	132	3	1	7.5	29	15116	43	15	0	256048	1.5	1000	No
91	67	F	363	11.1	524	32	14	Death	99.3	144	70	50	26	95	88	58	132	2.5	2.2	7.2	21	22661	36	15	0	512043	4.1	500	Yes
92	47	F	264	7.2	47	13	4	6	99.6	120	100	70	31	21	57	79	133	4	13	7.3	24	15791	43	15	0	112708	2	1500	No
93	58	F	293	7.6	113	14	3	8	101.7	120	130	90	25	21	50	81	129	4.2	1.6	7.36	22	17858	34	15	0	403695	1.5	1600	No
94	74	M	314	12.1	401	30	13	Death	101.7	144	70	50	32	90	59	98	137	3	2.5	7.35	23	21373	45	9	0	606728	4.4	600	Yes
95	55	M	315	7.9	116	15	3	7	101.7	119	130	90	25	21	52	81	131	4.2	1.6	7.3	23	18672	35	15	0	403502	1.4	1400	No
96	52	M	241	7.1	44	14	4	5	99.6	115	90	60	25	21	25	84	138	4.5	2.2	7.3	21	18281	40	15	0	310967	1.6	1500	No
97	61	M	310	8.3	220	21	6	15	100.8	140	150	100	27	21	67	91	132	3	2.5	7.22	19	11361	39	15	0	203463	5.1	500	No
98	71	F	293	12.7	395	31	12	Death	104.2	166	90	60	34	90	69	81	133	5.1	4	7.4	23	16653	32	11	0	205900	1.7	800	Yes
99	58	M	451	10.2	204	20	6	11	100.8	146	150	100	29	21	64	91	133	3.2	2.5	7.26	19	11272	40	15	0	212739	5	500	No
100	36	F	166	7.2	48	11	4	5	98.6	85	90	60	24	21	59	97	130	4	1.5	7.3	25	9425	36	15	0	123646	2.8	1500	No